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### A Spray Supplement Improves Sleep, Pain and Depression in Mild to Moderate Chronic Pain Patients

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#### Abstract

Chronic pain is an enormous global health problem, often co-existing with sleep disruptions and depressive symptoms. There is a growing interest and a need in alternative treatments to pharmaceuticals that address the complexities of chronic pain. In this study we tested the efficacy of an oral spray supplement product, consisting of melatonin, L-Theanine, 5-Hydroxytryptophan and a proprietary herbal extract. We assessed sleep quality, daytime sleepiness, pain, and depression. A retrospective study was performed by reviewing the charts of chronic pain patients from 40 to 65 years old in a chronic pain clinic who received an oral spray supplement (n=53) or no supplementation control group (n=39). The study aimed to assess changes in sleep quality, daytime sleepiness, depression, and pain via self-administered questionnaires using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Patient Health Questionnaire-9 (PHQ-9) and Brief Pain Inventory (BPI) respectively. Between the control and oral spray supplement groups, a significant difference was identified for all four parameters assessed. There was a significant improvement in PSQI change between the two groups (p=0.001). This was also mirrored in the ESS (p=0.001), BPI (p=0.001), and PHQ9 (p=0.001). The most significant changes were seen between study onset and one-week thereafter. The novel formulation of ingredients used as a treatment in this study improved sleep, pain and depression in insomnia patients in the setting of chronic pain.

**Keywords:** Chronic Pain, Insomnia, Depression, Anxiety

#### Introduction

Chronic pain is an enormous global health problem. Approximately 25.3 million American adults (11.2 percent) and 20 percent of the European population experience chronic pain, defined as consistent pain every day for the preceding 3 months or longer[1, 2]. Chronic pain is a complex condition, often co-existing with sleep disruptions and depressive symptoms. Additionally, sleep quality and difficulties initiating or maintaining sleep have been linked to worsening a person's depressive symptoms over time and contributing to the onset of chronic pain[3]. Insomnia, when examined alone, affects about 60 million Americans. Benzodiazepines or related Z-drugs are the most frequently used symptomatic treatments, but lack long-term effectiveness at the risk of developing tolerance and dependence[4, 5].

The multi-directional relationship between chronic pain, insomnia and depression further highlights the need to address all three of these conditions simultaneously for better treatment outcomes.

Effective treatment of chronic pain, insomnia and depression in clinic have almost always proven challenging with an urgent need for more optimal treatments that do not have the well-established adverse effects of anti-depressants, benzodiazepines, or opioids. Furthermore, we in our group have noticed a growing interest in searching for alternative and more integrative solutions such as dietary supplements and nutraceuticals.

In our clinic of over 300 chronic pain and insomnia patients, the subject of this research study was initially offered as a supplement and the positive anecdotal data sparked this study. A retrospective study was then designed and performed to assess the efficacy of an oral spray supplement in a volatile liquid form (spray) compared to a non-treatment group. We investigated the impact of this spray supplement on sleep quality, daytime sleepiness, pain and depression.

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## Material and Methods

### Study design

This retrospective study was designed to investigate the efficacy of an oral spray supplement (Dr. Spray's Somna Spray, manufactured by Spray Labs LLC, Phoenix, AZ) in diagnosed insomnia patients in the setting of mild to moderate chronic pain. In a chronic pain clinic, men and women aged between 40 and 65 years with a self-reported body mass index of 23 kg/m<sup>2</sup> +/- 5 were recommended to try the oral spray product to aid with insomnia and were encouraged to use the supplement for a minimum duration of four weeks. Subsequently, a chart review was conducted to assess changes in sleep quality, daytime sleepiness, depression, and pain via self-administered questionnaires using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Patient Health Questionnaire-9 (PHQ-9) and Brief Pain Inventory (BPI), respectively. In addition, a retrospective chart review was conducted to assess the same parameters in a similar group of patients who were not administered the supplement, referred to as the non-treatment control group.

### Patient Selection

In total, 53 qualified patients who were treated with the oral spray supplement and 39 patients in the non-treatment groups, were identified. Patients who had any evidence of secondary sleep disorder, such as general anxiety disorder and/or major depressive disorder were excluded from the study to make a primary insomnia treatment comparison between the supplement and the control group at the conclusion of the study. Patients with moderately severe to severe depression (PHQ-9 scores of 15 or above) were excluded. Patients with any medication changes, other than use of the oral spray supplement, during the last 4 weeks immediately prior to the study period and the 4 weeks during the study period were excluded. Patients who were on controlled-schedule medications including medications in the benzodiazepine or opioid groups as well as stimulants were excluded. Patients on any melatonin receptor agonists were excluded. Any patient who was not compliant with follow-up or demonstrated missed appointment visits was also excluded from the study.

### Study Groups

1. Oral spray supplement: 8 spray applications equaling 1.0 mg of melatonin, 0.75mg of L-Theanine, and 0.75mg of 5-Hydroxytryptophan (5-HTP). Other ingredients are present in minor concentrations

(Table 1). The spray was administered according to the manufacturer's recommended directions: 30 minutes before bedtime each night for the 4-week duration of the study.

**Table 1 Major and Minor ingredients in Oral Spray Supplement**

Ingredient	Amount (per unit of spray)
Melatonin	1.0 mg
5-HTP ( <i>Griffonia Simplicifolia</i> )	0.75 mg
L-Theanine	0.75 mg
*Additional ingredients include a proprietary blend of Cramp Bark, Feverfew, Ginkgo Biloba, Passionflower, and Skullcap	

2. Non-treatment control: Subjects were selected who did not have any medication changes and followed the criteria listed above to make an appropriate comparison to the supplement group.

### Sleep Quality

The PSQI is a self-administered, 19-item questionnaire that measures retrospective general sleep quality and disturbances over the past month[6]. It differentiates "poor" from "good" sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction during the last month. Scoring is based on a 0 to 3 scale with a score of 3 reflecting the negative extreme on the Likert Scale. The scores for the seven areas are summed to determine an overall, global score. A higher score indicates worse sleep and a global score of five or greater indicates a "poor" sleeper with a high degree of sensitivity and specificity. The PSQI has been widely used in clinical and research settings, and has also been used and validated in a variety of patient populations, including chronic pain patients[7-9].

### Daytime Sleepiness

The ESS is a simple, well-validated, reproducible questionnaire designed to measure the general level of excessive daytime sleepiness[10, 11]. The ESS is the most frequently studied and validated daytime sleepiness questionnaire and is widely used clinically to screen patients for the presence of daytime sleepiness and repeated after administration of treatment[12]. It is intended to measure daytime sleepiness that persists from week to week or longer in a given participant, independent of changes in time of day and from day to day. The ESS is an 8-item questionnaire with each item or situation scored from 0 (no chance of dozing in the situation) to 3 (high

chance of dozing in the situation). The final score is the sum of the 8 individual scores. A score of > 10 on the ESS is indicative of daytime sleepiness, with severity increasing with the score of up to 24. The test has excellent test-retest reliability, with a Pearson correlation coefficient of 0.82 ( $p < 0.001$ ) for 87 paired scores in one study[13].

### Depression

Depressive symptoms were assessed using the PHQ-9, which is a widely accepted and well-established method of assessing depression. The nine-item PHQ contains items derived from the DSM-V classification system pertaining to: (1) anhedonia, (2) depressed mood, (3) trouble sleeping, (4) feeling tired, (5) change in appetite, (6) guilt or worthlessness, (7) trouble concentrating, (8) feeling slowed down or restless, (9) suicidal thoughts[14]. Scores of 5-9 suggest mild depression, 10-14 moderate depression, 15-19 moderately severe depression, and 20 or above of severe depression.

### Pain

The BPI assesses the severity of pain and its impact on functioning. The questions include the location, pain medications, as well as amount of pain relief in the past week. The BPI is widely used in both research and clinical settings. It is a self-administered questionnaire that was originally designed to assess cancer pain[15, 16] and has recently been widely accepted as a generic pain questionnaire for other chronic pain conditions[17]. It is available in a short (9 items) and long (17 items) form. The BPI short form is more frequently used and is what is referred to when the BPI is cited in research, including in this study. The first, optional, item is a screening question about the respondent's pain on the current day. The questionnaire is then composed of pain drawing diagrams, four items about pain intensity (worst pain, least pain, average pain, pain right now), two items on pain relief treatment or medication, and one item on pain interference, with seven sub-items: general activity, mood, walking ability, normal walk, relations with other people, sleep, and enjoyment of life. Test-retest reliability has been assessed for malignant pain and shows good reliability for pain intensity ( $r = 0.8$ ) and pain interference ( $r = 0.8$ )[18]. Internal consistency of the BPI is high for the severity scale ( $0.81 < \alpha < 0.89$ ) and interference scale ( $0.88 < \alpha < 0.95$ )[19, 20].

### Patient Education

Daily use of medications and supplements were reviewed with patients at every weekly visit by the intake medical assistant as well as the attending physician. Responses to self-administered questionnaires were reviewed immediately before the visit by a medical assistant and during the visit by the attending physician to ensure consistency in treatment and compliance.

### Statistical Analysis

All statistical analyses were conducted using GraphPad Prism 6 (GraphPad Software Inc.). Individual group performances were compared after onset of the study using paired and un-paired t-testing. All Pearson correlation coefficients and respective  $p$  values were obtained through the use of correlation analysis incorporated within the statistical software package. An obtained  $p$ -value of less than 0.05 on the two-tailed t-test was considered to be significant.

## Results and Discussion

### Sleep quality

Sleep quality was assessed using the PSQI consisting of seven sub-components summed for a global score (Table 2). A higher score correlates to less optimal sleep. It can be noted that the control group demonstrated a change from baseline PSQI to conclusion of the study (mean $\pm$ SD) ( $12.2 \pm 1.19$  to  $12.9 \pm 0.82$ ,  $p = 0.001$ ).

Subjects receiving the supplement had a significantly larger reduction ( $6.05 \pm 1.04$ ) in the PSQI global score ( $p = 0.001$ ). The largest increase in sleep quality was seen from baseline to week 1 (Figure 1A). The control group improved ( $1.33 \pm 0.12$ ) as did the supplement group ( $3.57 \pm 0.07$ ) from baseline to week one. A two-tailed unpaired t-test revealed that the rates of change between the two groups from baseline to week 1 were significantly different (data not shown,  $p = 0.001$ ). Furthermore, regression analysis conducted at baseline and week 1 between the two groups revealed a significant difference between the slopes of the two generated lines (Control:  $Y = -1.333 * X + 12.18$ , Spray:  $Y = -3.566 * X + 11.89$ ,  $p = 0.001$ ). We also identified PSQI sub-components with the greatest correlation to the PSQI global score. Three sub-components with the largest correlation were sleep latency, sleep efficiency, and sleep duration ( $r = 0.694$ ,  $r = 0.474$ ,  $r = 0.401$ ). Table 2 displays paired-t-testing amongst all sub-components of the PSQI. Within the supplement group, a 55% change was seen in sleep-onset latency ( $p = 0.001$ ).

Table 2 Sleep-related parameters

	Control (n=39)			Supplement (n=53)		
	Baseline	Week 4	<i>p</i> value <sup>a</sup>	Baseline	Week 4	<i>p</i> value <sup>a</sup>
<b>Sleep quality</b>						
<b>PSQI Global (mean)<sup>b</sup></b>	12.2	12.9	<b>0.001</b>	11.9	5.85	<b>0.001</b>
<b>Duration of sleep (mean)<sup>c</sup></b>	1.85	1.95	0.210	1.72	1.02	<b>0.001</b>
<b>Sleep disturbance (mean)<sup>c</sup></b>	0.79	1.18	<b>0.001</b>	0.59	0.25	<b>0.001</b>
<b>Sleep latency (mean)<sup>c</sup></b>	2.64	2.85	<b>0.003</b>	2.60	1.15	<b>0.001</b>
<b>Daytime dysfunction (mean)<sup>c</sup></b>	2.03	1.85	<b>0.018</b>	2.00	1.00	<b>0.001</b>
<b>Sleep efficiency (mean)<sup>c</sup></b>	1.85	2.03	<b>0.018</b>	1.98	1.08	<b>0.001</b>
<b>Sleep quality (mean)<sup>c</sup></b>	2.00	2.03	0.571	2.00	1.38	<b>0.001</b>
<b>Need for medication (mean)<sup>c</sup></b>	1.03	1.03	-	1.00	0.32	<b>0.001</b>
<b>ESS total (mean)<sup>d</sup></b>	11.7	11.9	0.164	11.7	9.74	<b>0.001</b>
<sup>a</sup> <i>p</i> value of paired sample t-test between baseline and week 4						
<sup>b</sup> Total score can range from 0 (less difficulty) to 21 (more difficulty)						
<sup>c</sup> Score can range from 0 (less difficulty) to 3 (more difficulty)						
<sup>d</sup> Score can range from 0 (less difficulty) to 24 (more difficulty)						

### Daytime Sleepiness

Table 2 displays ESS data for the study groups. The control group did not demonstrate significant deviation from baseline to conclusion of the study ( $p=0.164$ ). However, daytime sleepiness in the supplement treatment group presented a significant change ( $1.96\pm 0.36$ ,  $p=0.001$ ). The reduction in ESS score continued throughout the study in the supplement group. Scores for patients in the control group did not present with a pattern. PSQI global scores were also correlated to ESS scores, which

yielded significant correlation with the supplement treatment, ( $r=0.36$ ,  $p=0.007$ ).

### Pain

The BPI survey does not have a cumulative sum as the PSQI or ESS, rather it contains two portions each with its own components: pain interference (PI) and pain severity (PS). Table 3 outlines the values from baseline to conclusion of the study. Patients in the control group did not demonstrate significant changes in either BPI category (PS:  $0.09\pm 0.45$ , PI:  $0.05\pm 0.21$ ). Patients receiving the supplement demonstrated a significant change (PS:  $0.40\pm 0.66$ , PI:  $0.58\pm 0.28$ ) in both sub-categories of the BPI.

Figures 1D and 1E illustrate similar rates of change as seen in the PSQI and ESS; the greatest changes for both components in the treatment group occurred from baseline to week one of the study; no significant change was seen in the control group. However, it should also be noted that from week one to conclusion of the study, the supplement group presented with no significant changes to either the PS or PI components ( $p=0.247$ ,  $p=0.124$ ).

Four categories of the BPI for the supplement group failed to demonstrate significant changes: average pain, pain now, interference with mood, and interference with sleep (Table 3). The three largest significant changes were interference with work, interference with walking, and interference with relationships (39.2%, 29.3%, 28.9%). It can be noted that these changes are

within the pain interference



Table 3 Pain and mood-related parameters						
	Control (n=39)			Supplement (n=53)		
	Baseline	Week 4	<i>p</i> value <sup>a</sup>	Baseline	Week 4	<i>p</i> value <sup>a</sup>
<b>Pain Severity Score<sup>b</sup></b>	2.47	2.56	0.217	2.99	2.59	<b>0.001</b>
<b>Worst pain (mean)<sup>b</sup></b>	3.33	3.44	0.571	3.76	3.02	<b>0.001</b>
<b>Least pain (mean)<sup>b</sup></b>	2.15	2.33	0.369	2.59	2.23	<b>0.001</b>
<b>Average pain (mean)<sup>b</sup></b>	2.56	2.62	0.689	2.81	2.55	0.051
<b>Pain now (mean)<sup>b</sup></b>	1.82	1.85	0.767	2.79	2.59	0.132
<b>Pain Interference Score<sup>b</sup></b>	1.75	1.80	0.171	2.54	1.96	<b>0.001</b>
<b>Interference with activity (mean)<sup>b</sup></b>	1.85	1.92	0.324	2.98	2.26	<b>0.001</b>
<b>Interference with mood (mean)<sup>b</sup></b>	1.95	2.03	0.183	2.04	1.91	0.089
<b>Interference with walking (mean)<sup>b</sup></b>	0.97	1.13	0.057	2.94	2.08	<b>0.001</b>
<b>Interference with work (mean)<sup>b</sup></b>	2.26	2.28	0.324	2.17	1.32	<b>0.001</b>
<b>Interference with relationships (mean)<sup>b</sup></b>	1.26	1.26	0.999	1.38	0.98	<b>0.001</b>
<b>Interference with sleep (mean)<sup>b</sup></b>	1.97	1.97	0.999	2.00	1.87	0.051
<b>Interference with enjoyment of life (mean)<sup>b</sup></b>	2.03	2.03	0.999	4.23	3.28	<b>0.001</b>
<b>PHQ-9<sup>c</sup></b>	10.1	10.1	0.812	9.89	7.13	<b>0.001</b>

<sup>a</sup>*p* value of paired sample t-test between Baseline and Week 4  
<sup>b</sup>Score can range from 0 (less pain) to 10 (more pain)  
<sup>c</sup>Score can range from 0 (less depression) to 27 (more depression)

score section of the BPI rather than the pain severity score section.

### Depression

Depression was assessed through the PHQ-9 questionnaire. Higher scores are associated with an

increased likelihood of depression. As shown in Figure 1C, there were no marked deviations in PHQ-9 score for control patients from study onset to conclusion. Paired-t-testing also indicated no significant change (Table 3). However, patients in the supplement group presented with significant changes ( $2.76 \pm 0.40$ ) from study onset to conclusion ( $p=0.001$ ). The greatest change in the PHQ-9 can be seen from baseline to week 1. Our findings also indicate that after the initial reduction in PHQ-9 score, no significant change can be seen from week 1 to study conclusion.

### Correlation Analysis: Sleep, Pain, and Depression

In order to assess whether one may cause an increase in the other, the mean change in the PSQI global score from baseline to week 4 of the study was correlated to the mean changes of both components of the BPI and the PHQ-9. No significant correlation was identified between the PSQI and PHQ-9. We did identify correlations of PSQI with pain severity ( $p=0.001$ ), but not pain interference ( $p=0.152$ ). In addition, a correlation in the supplement group was also identified between PHQ-9 and pain interference ( $p=0.018$ ).

According to The Third National Health and Nutrition Examination Survey conducted from 2003-2006, up to 49% of men and women in the United States utilize dietary supplements[21]. The effects of herbs and dietary supplements have been implicated in modulating glycemic control in diabetics, lowering serum cholesterol, and anxiety to name a few[22-24]. As of

1997, the latest point for which there is data, 46.3% of patients sought alternative medicine treatments and therapies. These findings are not solely isolated to the United States; a national study indicated that alternative medicine treatments are also used by Denmark, Finland, and Australia[25]. Although there

is not a more recent study, our anecdotal data suggests the use of alternative medicine is widespread.

In our chronic pain clinic of more than 300, patients are constantly looking for alternatives to pharmaceutical products. Thus, we conducted a study that sought to investigate the effects of an oral spray supplement on sleep quality, daytime sleepiness, pain, and depression. Effective treatment of chronic pain, insomnia and depression in clinic are almost always proven challenging with an urgent need for more optimal treatments that do not have the well-established adverse effects of anti-depressants, benzodiazepines, or opioids. Furthermore, as stated above, there is a constant large interest in searching for alternative and more integrative solutions such as dietary supplements and nutraceuticals. The multi-directional relationship between chronic pain, insomnia and depression further highlights the need to address all three of these conditions simultaneously for better treatment outcomes and solutions that may address all three.

### Sleep Quality and Daytime Sleepiness

Insomnia examined alone affects about 35% of the general population. Benzodiazepines or related Z-drugs are the most frequently used symptomatic treatments, but lack long-term effectiveness at the risk of developing tolerance and dependence[4, 5]. Furthermore, these drugs are associated with dementia and sleepwalking[26].

The supplement used in this study was seen to have profound effects on sleep quality and daytime sleepiness (Table 2). In comparison to controls, subjects receiving the spray supplement demonstrated a 50.8% improvement on the PSQI, the largest change occurring within one week after onset of the study. Daytime sleepiness was also assessed through the ESS questionnaire. We justified collecting data via ESS mostly due to the lack of evidence showing sleep quality and daytime sleepiness's correlation. One meta-analysis of various studies viewing potential relationships between sleep qualities assessed by the PSQI and daytime sleepiness assessed by the ESS indicated that the correlation between these two is insignificant. The parameters tested within the PSQI pertain to sleep quality, whereas those within ESS consider parameters of wakefulness[27]. Here, the comparison of the control group to the supplement treatment group displayed an initial decrease in both groups, however the supplement treatment group continued to display a

reduction whereas the controls did not (Table 2, Figure 1B). The supplement treatment group demonstrated a significant improvement ( $1.96 \pm 0.36$ ,  $p=0.001$ ) by the end of the study.

Of note, we were not able to locate previous studies correlating the effects of any of the listed ingredients with daytime sleepiness. We suggest that the sleep-promoting effects on sleep quality may have served to indirectly improve daytime sleepiness. When viewing the results for sleep quality and daytime sleepiness, it is important to consider the various ingredients that are present in the administered treatment.

Although we cannot isolate the study results and attribute them to a single ingredient, there are certain inferences that can be drawn. For instance, our data is consistent with previous studies that have identified patients with sleep deficiencies exhibiting reduced melatonin levels[28, 29]. Moreover, melatonin's role in regulation of the circadian rhythm in human subjects is well-established[30]. Clinical reviews have indicated that melatonin has a significant effect on various factors listed in the PSQI, such as sleep latency, sleep duration and sleep efficiency[31]. 5-HTP, another ingredient in the tested supplement, derived via *Griffonia simplicifolia*, undergoes enzymatic conversion to serotonin and is subsequently converted to melatonin in vivo[32]. It has been hypothesized that administration of 5-HTP can assist with re-regulation of sleep patterns and the circadian rhythm in patients. Moreover, studies have shown that injected radiolabeled 5-HTP serves as a direct precursor for the synthesis of endogenous melatonin[33]. Our data suggests that the administration of melatonin and its precursor, 5-HTP, through the oral supplement displayed similar effects. However, identifying the relative contributions to the improvement of sleep quality between these two compounds would require additional studies.

Valerian Root's two primary compound classes are valepotriates and sesquiterpenes[34, 35]. These compounds have been shown to significantly modulate sleep and have demonstrated anxiolytic properties[36, 37]. Pharmacologically, valerian root extract has been shown to activate benzodiazepine and GABA-like receptors in mice[38]. Coinciding with the effects of melatonin and 5-HTP in the supplement group, our data suggests that this mechanism may be contributory for the displayed effects on the PSQI (Table 2, Figure 1A).

### Chronic Pain

Chronic pain associated sequelae are not solely localized to a physical context. In addition, they also

consist of insomnia and depressive symptoms. Furthermore, sleep quality and difficulties initiating or maintaining sleep have been linked to worsening a person's depressive symptoms over time and contributing to the onset of chronic pain most likely by deteriorating central sensitization[3]. The relationship between chronic pain, insomnia and depression highlights the critical need to address all three of these conditions simultaneously for better treatment outcomes. The most common etiologies of pain in the United States have been associated with low back pain, headaches and migraines, neck pain, and facial aches,[39] costing the U.S. economy up to \$635 billion annually[40].

In the current study, the greatest reduction in pain occurred after study onset between baseline and week 1, mirroring similar patterns that were also seen in the PSQI and ESS (Figures 1D and 1E, Table 3). This analgesic effect of the supplement could be attributed to multiple components within the spray. The mechanism for melatonin's analgesic effects has not yet been clearly established but melatonin has shown a dose-dependent relationship with pain sensitivity and threshold[41]. The diurnal fluctuations in serum levels of melatonin have been correlated to pain sensitivity changes between daytime and nighttime in murine rats with a significant decrease seen during nighttime hours[42]. One study has shown that melatonin may not directly exert its effects on opioid receptors for pain reduction. Rather, melatonin has been surmised to indirectly mediate its analgesic effects through an increase of endogenous  $\beta$ -endorphin, which then act on opioid receptors[43].

Feverfew, an herb with leaves that can be consumed either fresh or dried, has been shown to mitigate the frequency of migraines in patients. Moreover, side effects pertinent to usage of this herb have been minimal[44]. Another ingredient in the supplement, which has shown efficacy treating cramp-induced pain and muscle tightness is valerian root. Valerian root contains chemicals that have been shown to induce hyperpolarization of the muscular membrane and impingement of calcium-mediated influx, leading to relaxation of muscular tissue[45, 46]. We propose that melatonin, in conjunction with feverfew and valerian root, may have mediated the reduction in PS and PI in our patients. In order to quantify the individual effects of each component, additional experiments would be necessary.

### Depression

Patients were also assessed for depression using the PHQ-9. Our data demonstrates a significant

improvement in depression for the supplement treatment group (27.9%,  $p=0.001$ ). The greatest change occurred immediately after the beginning of the study. The assessment of depression and other associated factors in this study, namely chronic pain and insomnia, is complex. In patients experiencing depression concomitant with chronic pain or insomnia, it is important to identify which condition precedes the other in order to establish better treatment guidelines. It is estimated that 30-54% of patients with chronic pain suffer from major depressive disorder[47]. Importantly, insomnia symptoms have been identified to be a predictor for 47% of cases of depression[48]. A report conducted by Riemann and Voderholzer analyzed data from various studies totaling  $n=29,480$  subjects. Their analysis arrived at the conclusion that patients presenting with insomnia-like complaints had an odds-ratio of 39.8 to develop depression within the next year[49].

Once an improvement in depression was established, we were interested in quantifying whether depression was more strongly associated with pain or sleep quality. Our results indicated that within the supplement group, there was a significant correlation between pain and depression in the pain interference sub-category of the BPI ( $r=0.325$ ,  $p=0.018$ ). Interestingly, PHQ-9 scores for the treatment group did not display a correlation of depression to the PSQI global score. A review conducted by Fishbain et al. identified two primary hypotheses regarding this matter, the antecedent hypothesis and the consequence hypothesis. These hypotheses predict depression as the precursor to chronic pain, or vice versa, respectively, with a large amount of data supporting both[50]. Sleep disorders have long been thought to be connected to mental health conditions[51]. Hypotheses regarding insomnia and depression indicate that a bidirectional relationship exists[52]. Evidence exists that supports melatonin's function as an N-Methyl-D-Asparate (NMDA) receptor antagonist and thus its modulating role in depression by decreasing the ionic flux through the NMDA receptor, which would mitigate depression symptoms[53]. Data from this study indicates that there was a significant difference before and after the study began.

Due to the aforementioned bi-directional hypothesis, it is difficult to identify if modulation of sleep and pain influences depression, or vice versa. The supplement used for this study contained other ingredients that have also been identified in improvements of depression. Skullcap, valerian root,

L-theanine, ginkgo biloba, and passionflower have all been implicated in improvements of depression[36, 54, 55].

Patients are increasingly looking for alternatives to pharmaceuticals for various reasons, including wariness for their common adverse reactions. Out of the 53 patients receiving the treatment in this study, we received no complaints or reports of any side effects. Taken together with the strong significant improvements in insomnia, pain and depression, we strongly suggest this supplement be considered for these conditions.

### Conclusion

The unique formulation of ingredients in the sleep supplement tested in this study contributed to significant improvements in sleep quality, daytime sleepiness, pain, and depression in comparison to a control group.

### Declarations

#### Abbreviations

5-HTP: 5-Hydroxytryptophan; BPI: Brief Pain Inventory; ESS: Epworth Sleepiness Scale; NMDA: N-Methyl-D-Aspartate; PI: Pain Interference; PS: Pain Severity; PHQ-9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index

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### Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

AA contributed to analysis and interpretation of data, drafting of the manuscript, and critical revisions of the manuscript. SR contributed to acquisition of data, critical revisions of the manuscript, interpretation of data, final approval of the manuscript, as well as study conception and design.

### Ethics approval and consent to participate

All participants in this study provided their written informed consent to participate in the study.

### Consent for publication

Not applicable.

### Competing interests

All authors state that there are no competing interests.

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**Figure 1 (A-E): Graphical Depiction of PSQI, ESS, BPI, and PHQ-9 data from baseline to conclusion of study**

Measurements were obtained for each patient every week for all self-reported patient questionnaires. A general trend can be identified in A, B, C, and E, with the largest significant change occurring from baseline to conclusion of the study. By study conclusion, significant decreases can be seen in various variables for patient's receiving supplement in comparison to controls.

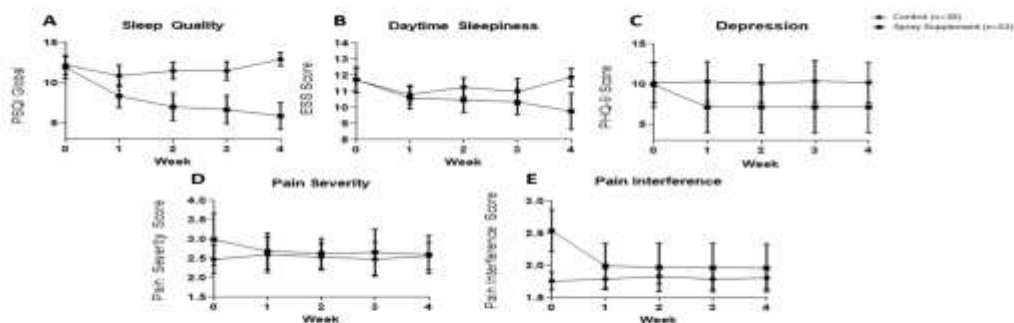


Figure 1 (A-E)

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