Role of Ashwagandha in Treating Bipolar Disorder

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Abstract

To see whether Ashwagandha root extract helps with sleeplessness and anxiety and if it's safe to use. The Prakruti Hospital in Kalwa, Maharashtra, India, undertook a randomized, double-blind, placebo-controlled trial. Using a 2:1 randomization ratio, a total of 60 patients were randomly assigned to one of two groups: either the experimental group (n = 40) or the control group (n = 20). Full-spectrum Ashwagandha root extract (300 mg) was the test product, whereas the placebo was a starch-based capsule similar to the test product. For a total of 10 weeks, both medications were given twice a day with milk or water. A substantial increase in quality of sleep was also found when the test was used in comparison to the placebo (p, 0.002). All other sleep indices, including as SOL, SE, PSQI, and anxiety (HAM-A scores), improved significantly after a 10-week therapy with Ashwagandha root extract. Sleep-inducing properties of Ashwagandha root extract, which is well tolerated and improves sleep quality in individuals with insomnia at a dosage of 300 mg extract twice day, have been shown. It has the potential to help individuals with insomnia and anxiety improve their sleep characteristics, but further large-scale trials are needed.

Keywords: *Ashwagandha, Insomnia, Anxiety, Sleep Onset Latency, Sleep Efficiency.*

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1. INTRODUCTION

Solanaceae family member Withania somnifera (L.) Dunal is often referred to as "Ashwagandha" because of its usage in Indian traditional medicine. Rasayana herbs, such Withania somnifera (WS), have a strong reputation in Ayurvedic medicine for rejuvenating the body and supporting the health of all tissues. This means that WS is also considered an adaptogen: a substance that supports overall body homeostasis by triggering multiple responses rather than just one particular method of pharmacological action. In addition to improving focus, memory and mood, WS is said to have the potential to protect against viruses and illness.

It is common for cognitive deficits to continue even when a person is experiencing euthymic mood in those with bipolar disorder (BD) (i.e., not manic or depressed). It is used in Ayurvedic medicine to help the body adapt to stress and fight sickness. Ashwagandha (Withania somnifera) is an adaptogen. Several types of neurologically bioactive ingredients in Withania somnifera extract (WSE) have been proven in animal models to correct memory impairments and enhance cognition. Patients with bipolar illness who were presently stable were the focus of this randomized, placebo-controlled, double-blind research (trial NCT00761761 registered at clinicaltrials.gov).

People with bipolar disease have extreme mood fluctuations that might range from exuberance to sadness. There are several symptoms and expressions that may vary widely based on the individual's constitution, environment, and imbalances. High vata (the biological principle of movement and dryness) is associated with bipolar illness in those who are prone to it since it is exacerbated by low ojas (immunity, strength, satisfaction, and capacity to cope). The Ayurvedic approach to treating this ailment includes a variety of natural tools and methods that may help patients regain their health and reduce their reliance on conventional medicine.

Schizophrenia often manifests as symptoms of depression and anxiety. Approximately 80 percent of schizophrenia patients have experienced depression at some point throughout their disease. 1 Even while depression may occur in chronic phases of schizophrenia, it may be more common in acute exacerbations, with rates ranging from 22% to 80% at this period. 2 Nearly 40% of schizophrenia patients have a concomitant anxiety spectrum disorder, making anxiety a prevalent symptom of schizophrenia. 3 As well as depressive

symptoms, anxiety is a typical symptom of schizophrenia and is more prevalent during acute psychotic episodes.

There are several traditional medical systems that make use of Withania somnifera (WS), most popularly known as Ashwagandha. Worldwide, WS has witnessed a rise in popularity because of its reputation as an adaptogenic herb. Because of its growing ubiquity, researchers have begun looking into the drug's biological effects, including the possibility of using it to treat neurological illnesses like schizophrenia and dementia.

Asthma, asthma, goiter, and ulcers are among of the ailments for which WS formulations have traditionally been used. They are also used for anxiety, sleeplessness, and neurological problems. The adaptogenic, anti-stress, and anti-inflammatory effects of the plant are connected to these usage [6, 7]. India and other countries now have an abundance of WS commercial items at their disposal. The Food and Drug Administration (FDA) classifies WS products as "botanical dietary supplements" in the US. WS is included in more than 1,300 goods on the US market, according to the Office of Dietary Supplements of the National Institutes of Health [8]. After falling to the 8th spot in 2016 [10], WS climbed to the 6th spot in 2017 [9]. As of 2019, WS was the 5th most popular dietary supplement, selling for over $10 million via mainstream channels (such as groceries and medicine shops) and more than $13 million through natural channels (such as the internet) (e.g., supplement and specialty retail outlets)

Common brain disorders

Emotional problems may also fall under the umbrella of "brain disorder," which covers insanity and other mental diseases. Emotional components, when they transcend the normality line, can create mental illness syndromes. The brain is said to have 100 billion neurons, each of which connects to a network of others. These nerve cells provide a variety of functions, including thinking, learning, and recalling……

Signs and Symptoms (Rupa and Laksana)

For those suffering from bipolar illness, there are times of euphoria (manic or hypomania) and periods of excessive depression that make everyday living difficult. Men are more likely than women to have bouts of euphoria or manic depression. People reach their highest risk of developing this condition in their early thirties.

In the euphoric and vata phases of bipolar disease symptoms include excessive talkativeness, reckless spending, sexual overindulgence, and frantic thinking (of money, time, energy). Overconfidence, irritation, hostility or rage aimed towards others, lack of sleep, and hyperactivity are some typical manic and pitta-type symptoms. When bipolar illness is in the depressed (more kaphic) phase, people experience low moods and a lack of interest in pleasure-seeking activities as well as excessive sleep and hypoactivity. There are characteristic vata, pitta and kapha symptoms, however a depression might be largely controlled by vata, pitta or kapha, for example. “ "If anxiety is caused by vata, then sadness must be caused by kapha, since it is heavy," many people believe. That's true, but it's not always the case. In fact, severe depression tends to be more of a vata disease," he continues. Suicidal thoughts and thoughts of self-harm are all vata signs of depression, as are feelings of helplessness, hopelessness, inability to concentrate or make choices and a host of other symptoms. Patients' cases are made distinctive by the fact that the symptoms indicated below might show up suddenly or develop over time in a variety of ways.

Ayurvedic Treatment

Ayurveda aims to alter the mind's energetics in order to treat any mental illness. Our ojas and stresses play an important role in Ayurveda's treatment of bipolar illness. As our capacity to deal with and tolerate the world's stresses grows, so does our tendency to experience mood swings of extreme highs and lows. If our ojas is powerful, we are less vulnerable to the doshas' whims. The more we detect and lessen our stresses, the less our ojas will wear down. The patient's therapist and family members are excellent partners in helping the patient identify these stresses. One of the most effective ways to control one's thoughts is to employ "diet and herbs for the physical plane; prana and the senses for a subtler plane; mantra and meditation for the level of one's own mind."

The first step in balancing the doshas is to focus on balancing vata, regardless of any other imbalances. Rather than just treating the existing state of vikruti, the practitioner aims to shift one's state of mind. A large number of

vata-relieving therapies also serve to strengthen ojas, and this is no accident. The most important thing to do for both is to establish regular, stable routines. This includes: waking and sleeping patterns, mealtimes and food selections, job schedules, and general daytime activities. Our body's capacity to perform at its peak is strained by irregular patterns. Regular bedtimes and mealtimes are two good instances of this. When our body's biological clock can forecast when we will eat or sleep, it will produce digestive enzymes, pepsin, and acid, as well as sleep-inducing melatonin. We are more likely to suffer from indigestion and sleeplessness if our bodies are prone to irregularity, which puts a lot of stress on our bodies and reduces ojas. Even more so since samana vayu, which we discovered as the fundamental cause of mood shifts and digestive tract doshas, is also the principal source of all doshic disturbances in the body, is particularly relevant to digestion. It's also crucial to get enough sleep. As a general rule, it is best to go to bed about 10pm and get up around 6am to allow the body to transition into the more stable kapha state. Meditative and physical exercises should be part of a regular morning regimen. All treatments must include attributes that counterbalance vata's characteristics of "cold bright mobile dry and piercing" in order to be effective. Regardless of the type of treatment, a focus should be placed on warm, heavy, stable, moist, oily, and dull qualities.

The most important thing to remember when it comes to eating is to eat at regular intervals throughout the day and never skip meals. In order to ground the patient and build up ojas, the diet should focus on whole grains and cooked vegetables, mung beans, meats, fresh dairy, nuts, and oils. It's best to accentuate the flavors of sweet, sour, and salty dishes, as well as the comforting aspects of hot, wet, and heavy fare. Cooler and blander foods can be useful during a pitta manic phase, while spicier food can be used during a depressive state. Preservatives and preservative-laden foods should be avoided. Stabilizing blood sugar levels are also critical. Increase the amount of fat and protein in your diet and limit the amount of simple carbs. Avoiding caffeine and other stimulants will help prevent a vata imbalance because they will keep you going artificially without allowing you to truly rest. When it comes to eating, lunchtime should be the most important meal of the day. In order to allow enough time for food to settle and digest, a meal should last at least an hour and be taken every day at the same time in a quiet, distraction-free environment before moving on to other activities. Before eating, say a prayer of thanks or a blessing to help center your mind.

Nervine tonics play a critical role in the herbal treatment of bipolar disorder because they promote mental equilibrium and well-being. While nervine sedatives and stimulants may be helpful in manic or euphoric episodes, the goal is not to force the brain out of a particular episode by giving herbal "upers" or "downers," but rather to provide herbal "upers" or "downers." While it's fine to have sedatives and stimulants on hand, the goal should be to balance the doshas and normalize the production of neurotransmitters by using tonics. The patient's constitution and current status should be taken into consideration while selecting a treatment formula. Ashwagandha, brahmi, shatavari, ginseng, shanka pushpi, nutmeg, skull cap, kappikacchu, haritaki, and bhringaraj are also effective tonic herb selections. All of the above may also be helpful for certain people; however, it's important to note that not all of these herbs are appropriate for everyone. The moderate stimulant and sedative properties of brahmi make it an excellent option for a wide range of mood disorders, including depression, anxiety, and insomnia. This herbal supplement is excellent for boosting ojas and soothing the nervous system, as well as calming the mind. Herbs that promote digestion and absorption should be taken with all of these herbs, as well. The combination of three fruits known as triphala not only helps to alleviate intestinal vata, but it also aids in the absorption of other medicines and foods being consumed, hence multiplying their benefits enormously. When it comes to dealing with bipolar illness, ghee is an excellent vehicle for allowing these medicines to permeate deep into the neural system.

2. LITERATURE REVIEW

Whirledge and Cidlowski, (2011), Hypothalamic–pituitary–adrenal (HPA) axis activation results in increased glucocorticoid (GC) production that suppresses the hypothalamic–pituitary–ovary (HPO) axis in response to stress. In order to avoid stress-induced changes in the female reproductive organs, it is possible to prevent stress-induced activation of HPA axis hormones or to limit their activities. This is because the ovary, the Fallopian tube, and the uterus are all affected by HPA axis activation.

Bhatnagar et al., (2015), Numerous therapeutic plants are mentioned in the Indian system of medicine. (Ayurveda). Turmeric (Curcuma longa), cinnamon (Cinnamomum verum), tulsi (Ocimum sanctum), ashoka (Saraca ashoka), ginger (Zingiber officinale), black cumin (Nigella sativa), papaya (Carica papaya), stinging nettle (Utrica dioica), tea plant (Camellia sinensis Linn), black pepper (These two herbs, the ashwagandha Withania somnifera and the vacha Acorus calamus, have a broad range of medical characteristics that are freely accessible. As the name implies, W. somnifera is also known as Indian Winter Cherry or Indian Ginseng. Ashgandh, asagandha, asana, asgandha, asundha, asvagandhi, pevette, sogade-beru, amkulang-kalang, etc. are

some of the numerous names it is known by in Indian languages. African, Mediterranean, and Indian regions are home to the tiny, woody shrub known as ashwagandha, which may reach a height of 2 feet or less. This evergreen plant may be found all throughout India's drier regions.

According to Singh et al. (2011), A. calamus is another often utilized plant. The common name for this plant is vacha, but it is also known as sweet flag, beewort, bitter pepper root, calamus root, flag root, gladdon, myrtle flag, myrtle root, myrtle sedge, pine root, rat root, German ginger, sea sedge, sweet cane, sweet cinnamon, sweet grass, sweet myrtle, sweet root, sweet rush and sweet sedge. Long, slender, upright, and scented leaves sprout from the rhizome of the semiaquatic perennial plant, Vacha. Sub-Tertiary areas may expect to see it.

Devaki et al. (2016), The vacha's antioxidant properties have also been shown. A. calamus extracts administered to rats exposed to noise restored SOD, GPx, and CAT activity in various parts of the brain (Manikandan et al.,). Free radicals were scavenged in a concentration-dependent manner by an extract of vacha in vitro (Sandeep and Nair). A benzene extract of the vacha rhizome reduced the oxidative stress caused by forced swimming and restraint in rats' plasma, as shown in both in vitro and animal tests.

Gupta SK. et al., (2013), Rosa canina hips aqueous extract reduces stress-induced changes in estrous cyclicity and ovarian and uterine weight. But none of these studies focused on different aspects of ovarian activity, such as follicular development, steroidogenesis, and antioxidant defense in conjunction with ovary dependent estrous cyclicity and accessory reproductive organs on one hand and adrenocortical activity on the other, to evaluate the efficacy of herbal extracts. As a result, more research into the effects of herbal extracts on stressed rats' ovaries is required. There hasn't been any research to yet showing that a herb-derived substance may alleviate stress's effects on the ovaries and other reproductive organs.

3. MATERIALS AND METHODS

Study objectives

We wanted to see how Ashwagandha root extract and a placebo affected the SOL, which we measured using actigraphy. Additionally, we'll look at the effects of Ashwagandha root extract on things like total sleep time (TST), wake time (WASO), and sleep efficiency (SE) using actigraphy; sleep quality (PSQI), mental alertness, and sleep quality (Sleep logs) using sleep logs; and anxiety score (HAM-A) using the Hamilton-Anxiety (HAM-A) scale as part of the secondary goals of the study (Figure 1).

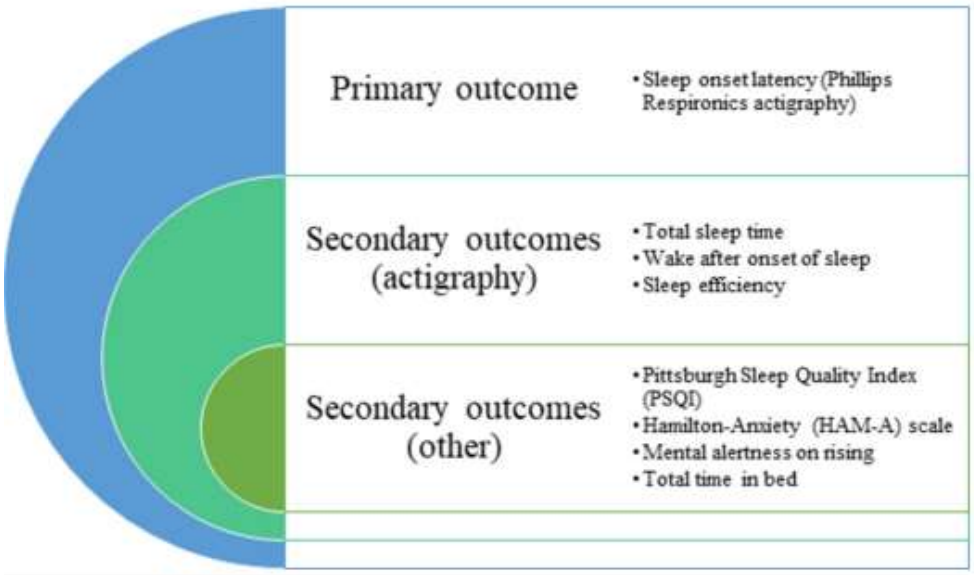

Figure 1: Study outcome measures

Study participants

There were 60 competitors in all, ranging in age from 18 to 60. An invitation was sent to research participants

who had been recruited from a variety of outpatient clinics (Prakruti Hospital, Kalwa, Thane, Mumbai, India). Participants were made aware of the investigation and were subjected to eligibility screenings by the lead investigator. The research included both male and female patients who were diagnosed with insomnia using the Diagnostic and Statistical Manual (DSMIV) and were above the age of 18 but under the age of 60.

Statistical analysis

At baseline, week five, and week ten, all of the study participants' data was gathered in accordance with the protocol. Randomized data were evaluated according to their randomized group, regardless of whether the therapy was followed or any other departure from the protocol was observed. Stata IC/13, a Windows-based statistical application, was used for all statistical analyses (StataCorp LLC, USA). Both ITT and PP datasets were used for the research. Intent-to-treat Means with one standard deviation (SD) and 95 percent confidence intervals (CIs) are shown here for the analysis results and scores produced (CI). The Friedman test (repeat measures) was used to compare baseline and post-treatment results for the various scales. The one-way analysis of variance was used to examine the differences between the two groups (ANOVA). Two-tailed tests with alpha 0.05 were used for all of the testing.

4. DATA ANALYSIS AND RESULTS

There were 85 participants in the first screening process, and 25 of them were deemed ineligible. Following randomization, the remaining 60 individuals were divided into two groups: the experimental and control groups, each with a 2:1 split. There were two withdrawals from the trial, one from each group, for non-compliance with actigraphy. Data from the remaining 58 subjects were analyzed using per-protocol (PP) analysis in order to complete the study.

Demography

Demography of the patients is presented in Table 1.

TABLE 1: Demography of patients enrolled

	Ashwagandha			Placebo			ANOVA	
	Mean	SD	95% C.I.	Mean	SD	95% C.I.	F	p
Intent-to-treat (ITT) dataset (n = 60)								
N	40			20				
Age (yrs.)	38.83	5.00	37.23 - 40.42	40.00	6.21	37.09 - 42.90	0.626	0.432
BMI (kg/sq.m)	26.91	3.42	25.81 - 28.00	25.89	6.02	23.07 - 28.71	0.695	0.408
Per-protocol (PP) dataset (n = 48)								
N	39			19				
Age (yrs.)	38.97	4.97	37.36 - 40.59	40.05	6.37	36.98 - 43.12	0.498	0.483
BMI (kg/sq.m)	26.87	3.46	25.75 - 28.00	25.28	5.50	22.62 - 27.93	1.834	0.181
		No.	%		No.	%		p
Gender (M/F)								
ITT dataset		31/9	77.5%/22.5%		16/4	80.0%/20.0%		0.8261
PP dataset		31/8	79.5%/20.5%		4	78.9%/21.1%		0.9263

PSQI outcomes

The test group had greater PSQI score changes than the baseline values at the conclusion of the trial. The baseline PSQI score for the test group was 13.07 (1.51) at the beginning of the trial and 9.15 (1.82) at the

conclusion. In contrast, the control group's mean PSQI was 13.47 (1.38) at the start of the trial and 11.8 at the conclusion (1.46). As shown in Table 2, the baseline, fifth, and tenth week PSQI values for both groups can be seen. The PSQI scores of the experimental group were significantly lower than those of the control group. Figure 2 shows that the PSQI scores for both groups gradually decreased over time. Treatment with Ashwagandha root extract powder showed superior results than placebo, according to the comparative measure.

TABLE 2: Sleep quality (PSQI) scores

	Ashwagandha (n = 39)		Placebo (n = 19)		ANOVA	
	Mean (SD)	95% C.I.	Mean (SD)	95% C.I.	F	Sig.
Baseline	13.08 (1.51)	12.59 - 13.57	13.47 (1.39)	12.80 - 14.14	0.927	0.340
5 weeks	10.85 (1.71)	10.29 - 11.40	12.63 (1.50)	11.91 - 13.35	15.054	<0.0001
10 weeks	9.15 (1.83)	8.56 - 9.75	11.84 (1.46)	11.14 - 12.55	31.221	<0.0001

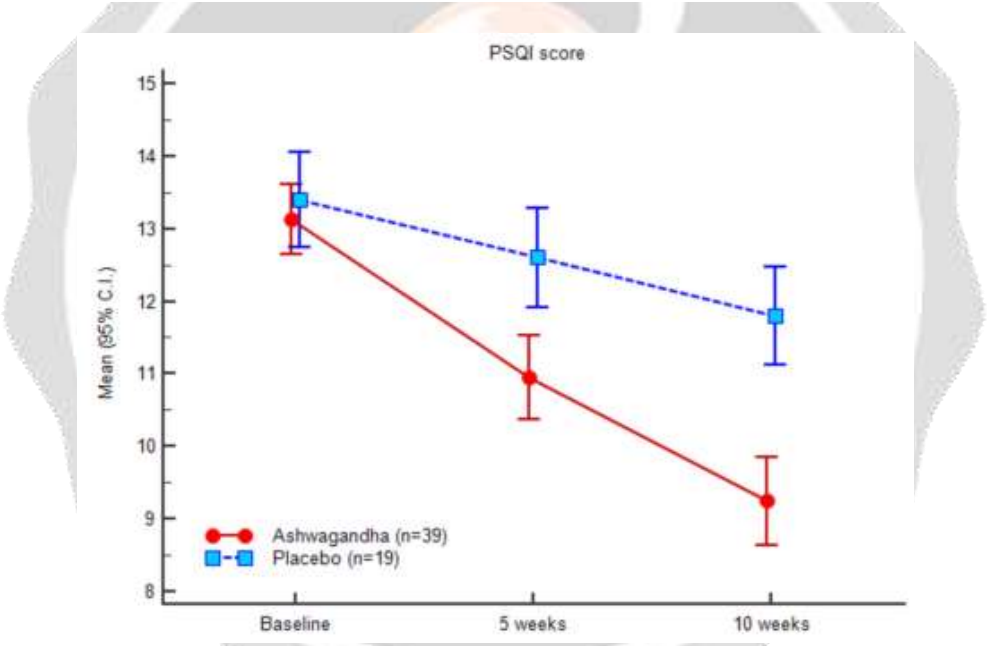

FIGURE 2: Pittsburgh sleep quality index (PSQI) scores

5. DISCUSSION

Modern urban living and other social and economic developments have made insomnia a major worldwide health issue. Associated stress, sleep apnea, and hormone imbalance are listed as the primary causes of insomnia in the most current worldwide study. Initial symptoms of chronic insomnia include chronic exhaustion, endocrinological disorders, energy depletion, and a lack of focus that may lead to a variety of health problems, such as high blood pressure or depression or renal disease or cognitive impairment or diabetes. Sleep deprivation and increased everyday stress are the primary causes of insomnia. An examination of the patient's medical history may help uncover the causes leading to the illness state, and behavioral therapy was also suggested by Buysse as a possible therapeutic option for insomnia.

The current therapy choices for insomnia are limited, and medical practitioners have tried a variety of approaches in an effort to alleviate the problem. Treatment options include anything from traditional medications like antipsychotics and antidepressants to cognitive behavioral therapy for insomnia (CBT-I),

precision medicine, and complementary and alternative medicine. Nonpharmacological therapy, bedtime limitation, and the use of receptor antagonists in connection to the orexin system for sleep-onset insomnia were previously tried as ways to deal with chronic insomnia [25,26]. For chronic or sleep-onset insomnia, none of these approaches proved to be a permanent fix. Rebound insomnia and withdrawal are common side effects of traditional sleep medicines, whereas cognitive deterioration is more common in the elderly. In this aspect, alternative medicine may be a viable option. Various approaches to alternative medicine, including the use of herbal items in customized therapy trials, have been advocated.

Herbal medicines have emerged as a promising alternative to conventional treatments for insomnia. Ashwagandha is one of a handful of herbal sources that have demonstrated promising results. Ashwagandha and the ancient Ayurvedic method worked together to achieve the intended outcome [28]. Ashwagandha has been shown to be safe and effective in clinical research for a variety of conditions, including stress and anxiety, cardiovascular endurance, and more.

For the first time, a clinical investigation has been carried out to investigate the impact of Ashwagandha root extract on the quality of sleep in the sampled population of patients. In a randomized, double-blind, controlled clinical experiment, the results were compared to those of a placebo and various sleep and anxiety metrics throughout the course of a 10-week treatment period. Participants with insomnia who took Ashwagandha root extract had significant improvements in sleep quality, sleep onset latency, and decreased anxiety compared to those who took a placebo. Tryethylene glycol, an active component in Ashwagandha leaves, has been shown to promote sleep in rats by delaying the beginning of NREM sleep.

Significant improvements in sleep indices SOL and SE as well as anxiety measures HAM-A have been shown to be a result of the current 10-week trial. Researchers discovered a significant difference between the Ashwagandha treatment group and the placebo group, indicating that Ashwagandha was effective in increasing sleep quality and lowering anxiety in the test participants.

The Western Psychiatric Institute and Clinic-University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, recruited 60 outpatients (18-60 years old) with a diagnosis of bipolar I, II, or not otherwise specified (NOS) illness for this research. A YMRS or MADRS score below 10 for at least four weeks was required, as was the usage of a steady dosage of the patient's primary mood stabilizing medication throughout that same time period. For example, patients with various neurologic illnesses; unstable medical circumstances or mental state; ashwagandha allergies or adverse reactions; cholinesterase inhibitor use, St. John's wort (Hypericum perforatum), or omega-3 fish oil; and pregnant or lactating women were not allowed to participate.

The WSE Sensoril®, a standardized investigational new drug (IND) was utilized in the trial (Natreon Inc.; New Brunswick, New Jersey). Using an aqueous extraction procedure, the WSE was concentrated to a minimum of 8% withanolides, 32% polyols, and 2% Withaferin A, and packaged in 250 mg hard gel capsules. The WSE has been shown to provide a wide range of health benefits. After being put in a container with WSE-infused fabric sachets for many days, the inert excipient placebo capsules were given the same aroma as the active placebos.

Over the course of eight weeks, patients were randomly assigned to receive either a placebo or WSE at doses of 250 mg daily or 500 mg daily, depending on their response to treatment. The patients' normal mood-stabilizing medication was not modified in any way or form. There were two sets of cognitive tests: the Set Shifting and Strategic Target Detection tests at the beginning of the study and the Flanker and Word List Memory tests at the end of it. These tests measured executive functioning, processing speed, attention, working memory, memory, and psychomotor speed. The Penn Emotional Acuity Test was used to assess students' social cognition. Anxiety disorders were measured by using the Hamilton Anxiety Rating Scale (HAM-ARS), the YMRS, and the MADRS (HARS).

The two organizations had a lot in common when they started out. According to the mean scores of the YMRS, MADRS, and HARS, the population was neither manic or depressed throughout the research. WSE dosage was reduced to 250 mg/day in two patients who reported vivid dreams (n = 1) and drowsiness (n = 1), respectively. To alleviate an individual's concerns of too vivid dreams, the dosage was decreased in the placebo group. Adverse events occurred in all groups at about the same rate. All of the side effects were minor and short-lived. Laboratory indicators, respiration rate, pulse, blood pressure, and body weight did not vary significantly. There was no significant difference in pill count compliance across groups, with 82.9 percent to 100 percent.

All of the test findings remained unchanged after four weeks. For the WSE group, the mean digit span backward test (Auditory Digit Span, $P = 0.035$) and the neutral mean response time (Flanker Test, $P = 0.033$) as well as the

mean social cognition response rating (Penn Emotional Acuity Test, P = 0.045) improved significantly over the placebo group after 8 weeks of treatment. All four tests showed no significant differences between the two groups. An extended period of therapy may result in bigger and probably more diverse gains, according to the time effect. Compared to the placebo group, participants in the WSE group exhibited significant gains in just the cognitive domain (P=0.041) on the Functioning Assessment Short Test (FAST).

With regard to patients with bipolar illness, WSE enhances verbal working memory, according to the authors. The authors admit that the results don't support their original premise; they had hoped for more cognitive improvements. The results might be the result of a variety of factors. It's possible that the trial was not long enough, the impact may be different in a symptomatic group, and a different extract may provide different findings. As a result, no effective upper or lower dose limits for the WSE have been established, and its effects may vary across different groups (depending upon type of drug therapy, type of bipolar disorder, patient age, etc.). It's also possible to employ performance-based cognitive assessments rather than self-reports, according to the scientists. To further understand the influence of WSE on cognition in patients with bipolar illness, more study is needed to examine these characteristics.

6. CONCLUSION

The standard treatments for insomnia that are now available have been shown to cause drug dependence and other consequences. Sleep-inducing properties of ashwagandha extract are well tolerated and increase sleep quality and onset latency in individuals with insomnia when taken twice daily at 300 mg extract. As a result, sleeplessness and anxiety may be amenable to its use.

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