AshwaMind®

STUDY INVESTIGATORS

Dr Poorna Prasad S & Dr Shuba Rani M

STUDY CENTRE

Sri Venkateshwara Hospital, Kuvempu Nagara, BTM 2nd Stage, BTM layout, Bangalore – 560076, Karnataka , India.

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www.botanichealthcare.net
info@botanichealthcare.net

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PO Box 8522 Christchurch 8440 New Zealand
Ph: +64 21 155 1894
nz@botanichealthcare.net

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A randomized, double-blind, placebo-controlled clinical study to evaluate comparative clinical Efficacy and Safety of ASHWAMIND on Cognitive Function in Adult Subjects

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CLINICAL STUDY REPORT

A randomized, double-blind, placebo-controlled clinical study to evaluate comparative clinical Efficacy and Safety of ASHWAMIND on Cognitive Function in Adult Subjects

INTRODUCTION

Cognition is defined as 'the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses. It is in essence, the ability to perceive and react, process and understand, store and retrieve information, make decisions and produce appropriate responses. The cognitive functioning is therefore critical for day-to-day life, governing our thoughts and actions. We need cognition to help us understand information about the world around us and interact safely with our environment, as the sensory information we receive is vast and complicated: cognition is needed to distill all this information down to its essentials.

Cognitive decline is a common and feared aspect of aging. Cognitive impairment creates significant challenges for patients, their families and friends, and clinicians who provide their health care.[1, 2] As populations continue to age, the prevalence of dementia is expected to increase. Alzheimer's disease is by far the most common cause of dementia. The clinical course of dementia represents the challenges that this disease presents. There are no truly effective therapies for treating dementia, and the cost effectiveness of Cholinesterase inhibitors has been challenged.[3]

Neurocognitive deficits are now recognized as part of the fundamental disturbances in schizophrenia. Patients with schizophrenia have widespread, multifaceted impairments in many domains of cognitive functioning, including executive function, concentration, perceptual/motor processing, vigilance, verbal learning and memory, verbal and spatial working memory, and semantic memory. Cognitive deficits may represent a core pathophysiological feature of the illness because at the time of the first psychotic episode these impairments are very similar in profile and severity to those seen in patients with more chronic illness. These deficits are apparently present even before the onset of the first psychotic features of the illness and appear to worsen slightly as illness onset approaches. [10]

Currently available therapeutic options for treating cognitive impairment includes Acetylcholinesterase drugs, which are associated with significant amount of adverse effects on long term use including symptoms of overstimulation of the parasympathetic nervous system, such as increased hypermotility, hypersecretion, bradycardia, miosis, diarrhea, and hypotension.[4,5,6,7] Acetylcholinesterase inhibitors are contra indicated in patients with cardiac comorbidity, gastric ulcers and urinary retention conditions.

Complementary and alternative medicine has been used for the well-being of the general population, especially when conventional modern medicine has failed to deliver and has also been used at times in conjunction with conventional medicine to obtain synergistic effects. Ashwagandha has been used since many years for improving Memory and Cognitive Functions in traditional medicine.

LITERATURE REVIEW:

Withania somnifera, also known as ashwagandha, is an important herb in Ayurvedic and indigenous medical systems. In Ayurvedic medicine, Withania somnifera (Ashwagandha) is commonly being used for its broad spectrum of pharmacological actions. Ashwagandha is traditionally used as a Rasayana (tonic) that works in a holistic manner to promote overall health and vitality. Ashwagandha is known for its memory boosting and restorative functions and is also reported to reverse loss of memory in by promoting the neurogenesis and growth of brain cells. Similarly root extract of the plant and one of its active component Withanolide A has been shown to improve spatial memory and cognitive deficits in temporal lobe epilepsy and experimental model of stroke.[11]

The plant is known as "Medhya Rasayana" or mind rejuvenate, used in enhancing memory and overall brain functioning. The active principles of Withania somnifera sitoindosides VII-X and Withaferin A (glycowithanolides) have shown an antioxidant effect in the brain, which may be responsible for its diverse pharmacological properties. Several studies indicated that Withania somnifera possesses antioxidant, anti-tumor, anti-stress, anti-inflammatory, immunomodulatory, hematopoietic, anxiolytic, anti-depressive, rejuvenating properties and was found to play a significant role in the prevention of different CNS disorders, especially in the conditions of stress and neurodegenerative diseases, which includes Parkinson's and Alzheimer's disorders, tardive dyskinesia, cerebral ischemia, and also in the management of the drug addiction. It has a cognition promoting effect and was found to be useful in children with memory deficit and old age people with memory loss.[12]
In a study, Withania somnifera improves the cognitive capabilities of the brain by increasing the capacity of muscarinic receptors.[13]

CHEMICAL COMPOSITION OF ASHWAGANDHA

The biologically active chemical constituents of Withania somnifera include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins. Sitoindosides and acylsterylglucosides in Ashwagandha are anti-stress agents. Active principles of Ashwagandha, for instance the sitoindosides VII-X and Withaferin-A, have been shown to have significant anti-stress activity against acute models of experimental stress. Many of its constituents support immunomodulatory actions. The aerial parts of Withania somnifera yielded 5-dehydroxy withanolide-R and withasomniferin-A. [14]

STUDY OBJECTIVE

The objective of this clinical study to evaluate comparative clinical Efficacy and Safety of Ashwamind (Ashwagandha extract) in Cognitive Function in Adult Subjects.

OVERALL STUDY PLAN

Subjects with memory impairment were enrolled into study along with other inclusion/ exclusion criteria after obtaining Institutional Ethics Committee approval and Informed Consent, in writing. All 30 subjects were randomized into 2 groups and received Investigational product/Placebo in 1:1 ratio for 56 days as one capsule three times daily after food. Vital parameters, signs and symptoms monitored daily. Efficacy of investigational drug was evaluated with that of placebo in improving MMSE score done on each visit of the study. At the end of day 56 complete data analysis was done.

DOSE AND METHOD OF ADMINISTRATION

One 500mg soft gel capsule orally in the morning (after breakfast), one after noon (post lunch) and one in night (after dinner).

SELECTION & WITHDRAWAL OF SUBJECTS

Subject Screening

Medical history and demographic data including sex, age, body weight (kg), and height (cm), and habits were recorded during general screening of volunteers that was organized 1 day prior to study start. Each subject underwent a complete general physical examination and laboratory tests.

Inclusion Criteria

To qualify for enrollment in the study,

- Both male and female subjects aged between 40-75 years with a complaint of memory impairment for at least one year without any major cognitive deficit.
- Subjects who are willing to sign ICF

Exclusion criteria

The exclusion criteria are as follows:

- Subjects with Psychiatric disorders
- Subjects with alcohol consumption
- Subjects with any organ system infection in past 30 days
- Subjects with severe cognitive problems like dementia, function disability, post vascular cerebral symptoms or with any neurological problems

STATISTICAL ANALYSIS

The data generated in the clinical study will be analyzed by applying appropriate statistical method. Unless otherwise stated, all hypotheses will be tested at a significance level of 0.05 and 95% confidence interval. The Statistical analysis plan will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

STANDARDISATION

Each capsule of 500mg Ashwamind (Withania somnifera extract) contains withanolides NLT 2.5% and Withanolide A NLT 0.25% by HPLC.

RESULTS AND OBSERVATIONS

Demographics and baseline characteristics

Average age of subjects enrolled into the study was 57 years, approximately the same between both the groups at the time of screening. Total 15 males (50%) and 15 females (50%) participated in the study. Average BMI was 24.3 kg/m2, on the baseline visit.

Safety Results

There was no clinically significant abnormality observed in test and control group subjects inferring the active product is safe for administration. The safety parameters including ECG and laboratory tests (CBC, RFT and LFT) were within normal limits on screening and on day 56.

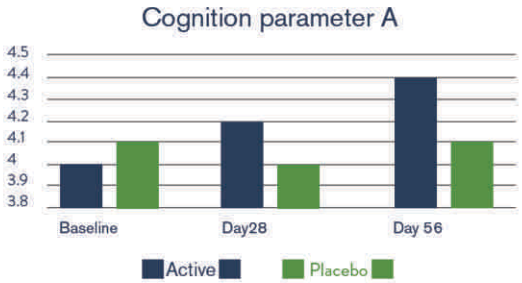
Efficacy Results

The Mini-Mental State Examination (MMSE) is the best-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research and community settings. Clinical features of Cognitive impairment are assessed in this study by MMSE scale. The MMSE is composed of 11 major items (sub scales); A- temporal orientation (5 points), B- spatial orientation (5 points), C- immediate memory (3 points), D- attention/concentration (5 points), E- delayed recall (3 points), F- naming (2 points), G- verbal repetition (1 points), H- verbal comprehension (3 points), I- writing (1 points), J- reading a sentence (1 points), and K- constructional praxis (1 points). The MMSE has maximum score of 30, with five different domains of cognition analyzed: (1) Orientation, contributing a maximum of 10 points, (2) Memory, contributing a maximum of 6 points, (3) Attention and calculation, as a measure of working memory, contributing a maximum of 5 points, (4) Language, contributing a maximum of 8 points, and (5) Design copying, contributing a maximum of 1 point. Individuals scoring two points below the maximum in any independent domain (except design copying) were considered to be impaired 15. Improvement in MMSE score in sub scale score and overall total score signifies improvement in cognitive function and effectiveness of therapy.

MMSE RESULTS: A- TEMPORAL ORIENTATION (MAX SCORE=5)

There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.046)

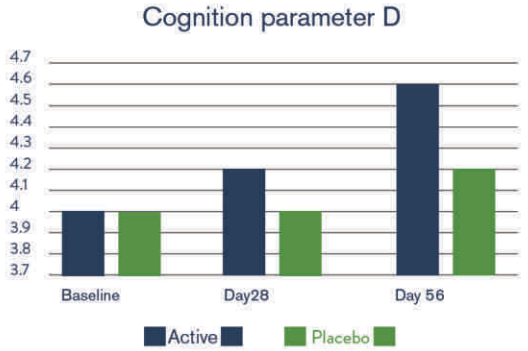
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
A	Baseline	4	4.1
	Day 28	4.2	4
	Day 56	4.4	4.1



MMSE RESULTS: D- ATTENTION/ CONCENTRATION (MAX SCORE=5)

There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.047)

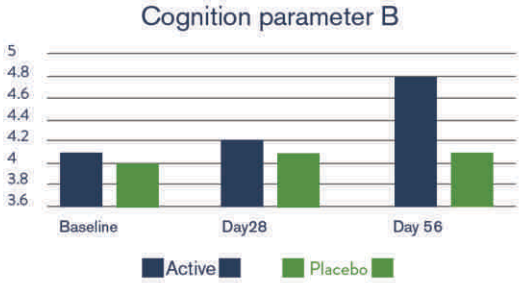
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
D	Baseline	4	4
	Day 28	4.2	4
	Day 56	4.6	4.2



MMSE RESULTS- B- SPATIAL ORIENTATION (MAX SCORE=5)

There was statistically significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.043)

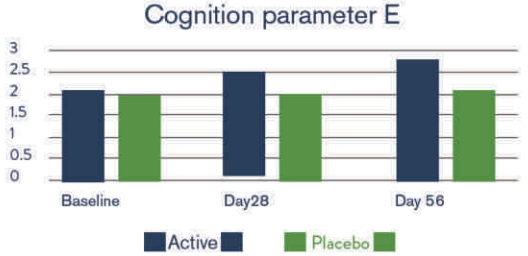
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
B	Baseline	4.1	4
	Day 28	4.2	4.1
	Day 56	4.8	4.1



MMSE RESULTS: E- DELAYED RECALL (MAX SCORE=3)

In active group mean score was 2.1 at baseline and 2.7 at day 56. In placebo group score was 2 at baseline and 2.1 at day 56. There was statistically significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.036)

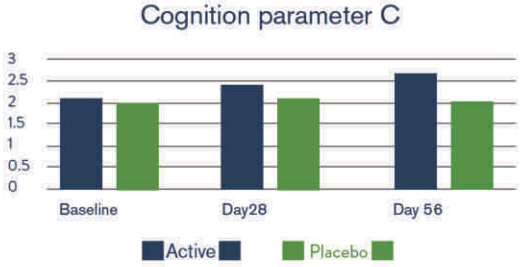
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
E	Baseline	2.1	2
	Day 28	2.4	2
	Day 56	2.7	2.1



MMSE RESULTS- C- IMMEDIATE MEMORY (MAX SCORE=3)

There was statistically significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.043)

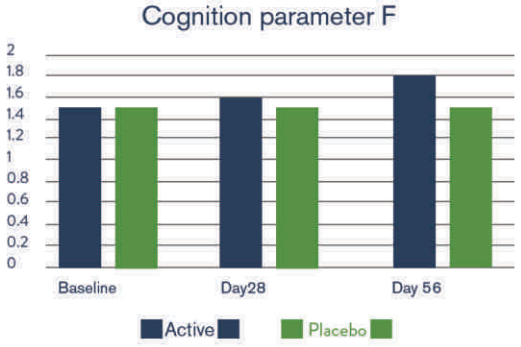
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
C	Baseline	2.1	2
	Day 28	2.4	2.1
	Day 56	2.6	2



MMSE RESULTS: F- NAMING (MAX SCORE=2)

There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.044)

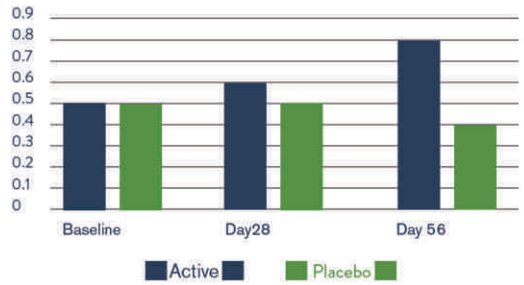
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
F	Baseline	1.5	1.5
	Day 28	1.6	1.5
	Day 56	1.8	1.5



MMSE RESULTS: G- VERBAL REPETITION (MAX SCORE=1)

There was significant improvement in mean score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.035)

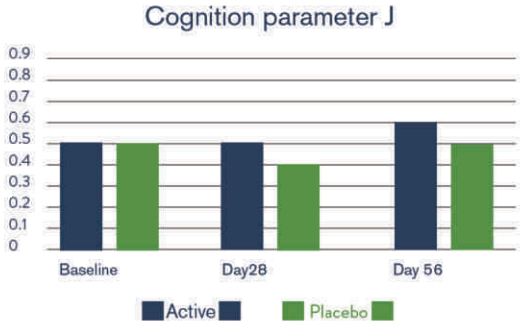
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
G	Baseline	0.5	0.5
	Day 28	0.6	0.5
	Day 56	0.8	0.4



MMSE RESULTS: J- READING A SENTENCE (MAX SCORE=1)

There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group. (P value = 0.047)

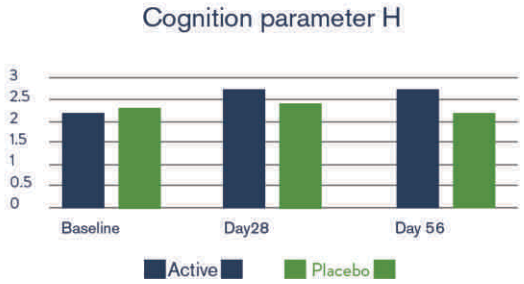
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
J	Baseline	0.5	0.5
	Day 28	0.5	0.4
	Day 56	0.6	0.5



MMSE RESULTS: H- VERBAL COMPREHENSION (MAX SCORE=3)

There was significant improvement in score in active group from baseline to day 56 in comparison to placebo group (P value = 0.048)

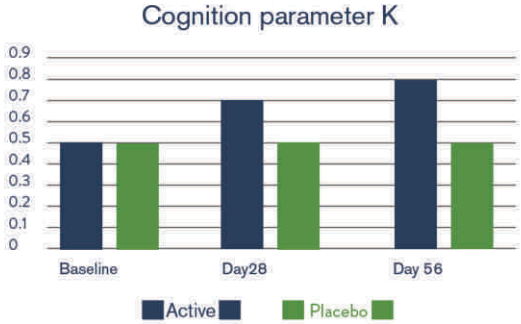
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
H	Baseline	2.2	2.3
	Day 28	2.7	2.4
	Day 56	2.7	2.3



MMSE RESULTS: K- CONSTRUCTIONAL PRAXIS (MAX SCORE=1)

There was statistically significant improvement in mean score in active group from baseline to day 56 compared to placebo group. (P value = 0.049)

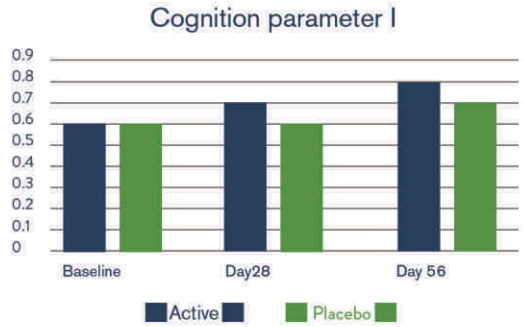
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
K	Baseline	0.5	0.5
	Day 28	0.7	0.5
	Day 56	0.8	0.5



MMSE RESULTS: I- WRITING (MAX SCORE=1)

There was improvement in score in active group from baseline to day 56.

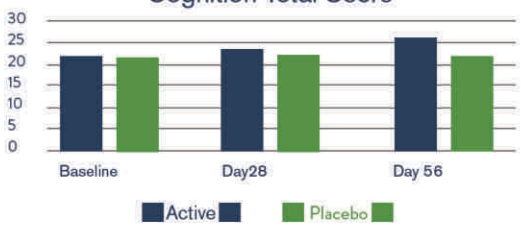
PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
I	Baseline	0.6	0.6
	Day 28	0.7	0.6
	Day 56	0.8	0.7



MMSE TOTAL SCORE (MAX SCORE=30)

The improvement in MMSE total score in Active group from baseline to day 56 was statistically significant. (P value = 0.048) compared to placebo group.

PARAMETER	VISITS	ACTIVE (Mean Score)	PLACEBO (Mean Score)
TOTAL SCORE	Baseline	22.1	22
	Day 28	23.7	22.1
	Day 56	26.6	22.4



CONCLUSION

Ashwamind (Ashwagandha extract) has demonstrated an excellent safety and efficacy profile in patients with cognitive impairment in present study. Patients had clinically significant improvement in symptoms by day 56 as evidenced by MMSE scores in test group. Subscale parameters in MMSE scale were also improved significantly in test group at the end of study indicating the improvement in symptoms of different domains of cognitive functions including naming, immediate memory, verbal comprehension, constructional praxis, delayed recall, temporal orientation, attention/concentration and spatial orientation. Treatment was well tolerated and there were no any serious adverse effects related to study medication. This clearly indicates that Ashwamind (Ashwagandha extract) is safe when administered orally and has definitive role in the management of cognitive impairment.

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