

A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY OF ASHWAGANDHA ON GENERALIZED ANXIETY DISORDER

Sud Khyati S. Thaker Anup B.

Department Kayachikitsa, International Centre for Ayurveda studies, Gujarat Ayurved
University, Jamnagar, India

ABSTRACT

Generalized Anxiety Disorder (GAD) is the most frequent anxiety disorder which comes across in the primary care settings. Pharmaceutical treatments for GAD are usually associated with various side effects hence herbs like *Ashwagandha (Withania somnifera)* can be used in managing this condition due to its anti-stress and anxiolytic activity. Considering all these points the present placebo controlled study was planned to assess the clinical efficacy of *Ashwagandha (Withania somnifera)* granules in the management of Generalized Anxiety Disorder. In Hamilton's Anxiety Rating Scale insignificant difference was found in both the groups except Anxious mood which showed a highly significant difference ($P < 0.001$). On the whole despite having insignificant statistical difference in both the groups, Group A, *Ashwagandha (Withania somnifera)* granules showed a better percentage improvement than Group B (Placebo).

Keywords: *Ashwagandha*, Placebo, Generalized Anxiety Disorder, Hamilton's Anxiety Rating Scale, Anxiolytic, Nootropic

INTRODUCTION

Generalized Anxiety Disorder (GAD) is the most frequent anxiety disorder which comes across in the primary care settings. It is associated with considerable economic costs owing to its low work productivity and high medical resource use.¹ Being an alarming disease, it requires effective management. In recent years several synthetic drugs have been introduced for the treatment of anxiety disorders. Though these drugs have good results but major side effects such as drug dependence, drug resistance, sedation etc. cannot be avoided *Ayurveda* is a great treasure of precious concepts like *Rasayana* (Rejuvenation therapy) which can be very

well utilized to combat with this burning issue. *Ashwagandha (Withania somnifera)* is one such drug which can be very well used as a *Rasayana* (Rejuvenation therapy) in managing this condition. It helps in Neuritic regeneration and synaptic reconstruction.² This herb known for its Immunomodulatory and CNS effects.³ It is well known for its anti-fatigue and anti-stress activity.⁴ Its anxiolytic activity is also well reported⁵

Considering all these facts the present clinical study was planned to assess the clinical efficacy of *Ashwagandha (Withania somnifera)* granules in the management of Generalized Anxiety Disorder and an effort to provide clinical evidence for anxiolytic effect of

Ashwagandha (*Withania somnifera*) was made.

MATERIAL AND METHODS

Study Design: Double blind randomized placebo controlled study.

Method of Generating Randomization

Sequence: Computer generated Randomization from www.randomization.com vide seed 23586 Randomization plan created on March 24, 2010 was used for the clinical study.

Method of drug preparation: The Dried roots of *Ashwagandha* were subjected to

pulverizer to get fine powder. Equal quantity of sugar was taken and syrup was prepared by adding sufficient quantity of water in mild flame with constant stirring till syrup reaches the *Tantumavam* (thread like) stage. Then *Ashwagandha* powder was added to the sugar syrup and mixed thoroughly to prepare a homogeneous blend. The blended mass was sieved through a 40# sieve to obtain granule form and kept it for drying in room temperature. Prepared granules were Stored in an airtight container in a cool dry place away from direct sunlight.

Table 1: Ingredients of *Ashwagandha* Granules

Drugs	Quantity
<i>Ashwagandha</i> roots	1 part
Sugar	1 part
Water	Q.S

In a similar manner Placebo granules were prepared out of Wheat flour.

Blinding

The Prepared drugs were blinded and labelled as Group A and Group B by the Department of *RasaShastra*, I.P.G.T&RA, Jamnagar.

Selection of Patients

Patients satisfying the Inclusion criteria were selected from the O.P.D & I.P.D of I.P.G.T.&RA Jamnagar irrespective of their sex, caste, religion, occupation and economic status. Patients were included in the study after taking a written consent.

Inclusion criteria

1. Patients fulfilling the DSM IV TR Diagnostic Criteria for Generalized Anxiety Disorder (300.02)⁶
2. Age group between 16-60 years

Exclusion criteria

1. Patients presenting with Major Organic Disorders and Psychotic Disorders
2. Patients below 16 years of age and above 60 years

3. Patients suffering from any other serious illness

Ethical clearance

Ethical clearance was obtained from Institutional Ethics Committee of Institute for Post Graduate Teaching and Research in Ayurveda, Gujarat Ayurved University, Jamnagar – 361008; Vide Ref PGT/7/Ethics/2009-10/3494/3

Source of monetary or material support

Institute for Post Graduate Teaching and Research in Ayurveda, Gujarat Ayurved University, Jamnagar- 361008.

Method of allocation concealment:

1. Selected patients were randomly divided into two groups by following the computerized randomization plan. (www.randomization.com vide seed 23586, created on March 24, 2010)
2. The Prepared drugs were blinded and labelled as Group A and Group B by the Department of *Rasa Shastra*, I.P.G.T&RA, Jamnagar

3. Total 101 patients of Generalized Anxiety Disorder were selected. Out of them 86 patients completed the treatment and they were placed into two groups viz Group A and Group B.

Grouping

Trial Group:

Drug: *Ashwagandha (Withania somnifera)* granules; Dose: 4 grams thrice daily; *Anupana*: Milk; Duration: 60 days; Follow up: 30 days

Control Group:

Drug: Placebo (Granules made from wheat flour was given as placebo which was identical to the trial drug); Dose: 4g thrice daily; *Anupana*: Milk; Duration: 60 days; Follow up: 30 days

Assessment Criteria:

Assessment was carried out before treatment, after treatment and after follow up period Hamilton's Anxiety Rating Scale.⁷ Clinical record proforma was prepared and on the basis of documentation proper statistical analysis was made for the assessment of the result of the trial drug.

Informed Consent:

An informed written consent was obtained from all included subjects before commencement of treatment.

Statistical analysis:

The information gathered on the basis of observations was subjected to statistical analysis. Effect of therapy of the subjective parameters was assessed based on the Wilcoxon's Signed rank test. Comparative effect of therapy was assessed on the basis of Chi square test. Students paired 't' test was applied for the objective parameters like hematological and biochemical investigations. All the tests were done with the help of software Sigma Stat 3.5.

Criteria for overall assessment of therapy:

The total effect of therapy was assessed considering the overall improvement in signs and symptoms. The obtained results were measured according to the grades given below:

Complete Remission: 100% relief

Marked Improvement : >76 - 99 %

Moderate Improvement : >51 – 75 %

Mild Improvement: >26 – 50 %

Unchanged : <25 % or No relief

Opening of the Blinding:

The sealed cover containing the information on blinding was opened by blinding committee on 14.11.11 after the statistical analysis of the collected data. On unmasking it was found that Group A consist *Ashwagandha (Withania somnifera)* granules and Group B consisted Placebo granules.

RESULTS AND OBSERVATIONS

Group A (*Ashwagandha (Withania somnifera)* granules): Forty four patients were treated in Group A for sixty days. *Ashwagandha (Withania somnifera)* Granules showed highly significant improvement ($P < 0.001$) in the parameters of Hamilton's Anxiety Rating Scale, *Ashwagandha (Withania somnifera)* granules provided a statistically highly significant improvement ($P < 0.001$) in symptoms like Anxious mood, Tension, etc. Maximum improvement was seen in respiratory symptoms i.e. 88.63% followed by muscular complains i.e. 83.67%, depressed mood i.e. 80.24%, sensory complains i.e. 78.79% and insomnia i.e. 77.31%. (Table 2).

Table 2: Effect of therapy on Hamilton’s Anxiety Rating Scale (Group A)

Symptoms	Mean Score		Mean difference	Relief %	S.D.	S.E.	W	P
	B.T.	A.T.						
Anxious mood	2.98	1	1.98	66.40	0.15	0.02	946	<0.001
Tension	2.67	0.76	1.91	71.30	0.36	0.05	946	<0.001
Fear	2.02	0.80	1.23	60.92	0.52	0.08	861	<0.001
Insomnia	2.25	0.51	1.74	77.31	0.50	0.07	903	<0.001
Difficulty in concentration & memory	1.95	0.88	1.06	54.76	0.41	0.06	861	<0.001
Depressed mood	1.88	0.37	1.51	80.24	0.60	0.09	903	<0.001
Muscular complains	2.28	0.37	1.90	83.67	0.42	0.06	946	<0.001
Sensory complains	2.30	0.48	1.81	78.79	0.39	0.06	946	<0.001
CVS	1.51	0.30	1.16	76.92	0.37	0.05	946	<0.001
R.S.	1.02	0.11	0.90	88.63	0.57	0.08	595	<0.001
G.I.T	2	0.91	1.09	54.65	0.48	0.07	820	<0.001
G.U.S	2.06	0.69	1.37	66.29	0.57	0.08	861	<0.001
Autonomic complains	2.09	0.53	1.55	74.45	0.50	0.07	946	<0.001
Behavior during interview	2.65	0.70	1.97	74.56	0.34	0.05	946	<0.001

Group B (Placebo granules): Forty two patients were treated in Group B for sixty days. Placebo Granules also showed highly significant improvement (P<0.001) in the symptoms of Hamilton’s Anxiety Rating

Scale with maximum improvement in muscular complains i.e.40% followed by depressed mood i.e.39.08% and 37.6% improvement in behaviour during interview. (Table 3)

Table 3: Effect of therapy on Hamilton’s Anxiety Rating Scale (Group B)

Symptoms	Mean Score		Mean difference	Relief %	S.D.	S.E.	W	P
	B.T.	A.T.						
Anxious mood	2.79	1.79	1.00	35.83	0	0	946	<0.001
Tension	2.65	1.74	0.91	34.21	0.36	0.05	741	<0.001
Fear	2.09	1.44	0.64	30.71	0.48	0.07	406	<0.001
Insomnia	2.16	1.37	0.80	36.55	0.411	0.06	595	<0.001
Difficulty in concentration & memory	1.68	1.41	0.23	13.89	0.42	0.06	66	<0.001
Depressed mood	2.02	1.23	0.80	39.08	0.41	0.06	595	<0.001
Muscular complains	2.09	1.25	0.83	40	0.43	0.06	630	<0.001
Sensory complains	2.16	1.58	0.58	26.88	0.50	0.07	325	<0.001
CVS	1.44	1.06	0.37	25.80	0.54	0.08	120	<0.001
R.S.	1.14	0.98	0.16	14.28	0.37	0.05	28	<0.001
G.I.T	1.93	1.49	0.40	20.48	0.49	0.07	190	<0.001
G.U.S	2.11	1.48	0.62	29.67	0.49	0.07	378	<0.001
Autonomic complains	2.09	1.37	0.72	34.45	0.45	0.07	496	<0.001
Behavior during interview	2.72	1.70	1.02	37.60	0.15	0.02	946	<0.001

Comparative effect of therapy on Hamilton’s Anxiety Rating Scale between both the groups shows that there was no significant difference (P>0.05) in any of the

symptoms except for Anxious mood which showed a highly significant difference (P<0.001). (Table 4)

Table 4: Comparison of Effect of Therapy on Hamilton’s Anxiety Rating Scale

Symptoms	Group A		Group B		X ² value	P value
	Mean difference	S.D.	Mean difference	S.D.		
Anxious mood	1.98	0.15	1.00	0	10.24	<0.001
Tension	1.91	0.36	0.91	0.36	8.46	=0.08
Fear	1.23	0.52	0.64	0.48	0.63	=0.73
Insomnia	1.74	0.50	0.80	0.41	1.01	=0.60
Difficulty in concentration & memory	1.06	0.41	0.23	0.42	1.41	=0.49
Depressed mood	1.51	0.60	0.80	0.41	0.64	=0.89
Muscular complains	1.90	0.42	0.83	0.43	1.57	=0.81
Sensory complains	1.81	0.39	0.58	0.50	0.02	=0.90
CVS	1.16	0.37	0.37	0.54	2.38	=0.30
R.S.	0.90	0.57	0.16	0.37	0.42	=0.81
G.I.T	1.09	0.48	0.40	0.49	1.09	=0.58
G.U.S	1.37	0.57	0.62	0.49	0.29	=0.86
Autonomic complains	1.55	0.50	0.72	0.45	0.01	=0.96
Behavior during interview	1.97	0.34	1.02	0.15	0.14	=0.93

Overall effect of therapy based on Hamilton’s Anxiety Rating Scale shows that there was moderate improvement in 29.07 %

of patients, mild improvement was seen in 60.46 % of patients and 10.46 % showed no change in the condition. (Table 5)

Table 5: Overall effect of therapy based on Hamilton’s Anxiety Rating Scale

Results	Group A (n=43)		Group B (n=43)		Total	
	No.	%	No.	%	No.	%
Complete remission (100%)	0	0	0	0	0	0
Marked improvement (>75-100%)	0	0	0	0	0	0
Moderate improvement (>50-75%)	25	58.13	0	0	25	29.07
Mild improvement (>25-50%)	17	39.53	35	81.39	52	60.46
Unchanged (<25%)	1	2.32	8	18.6	9	10.46

DISCUSSION AND CONCLUSION

Ashwagandha (*Withania somnifera*) granules have provided highly significant improvement on almost all parameters of Hamilton’s Anxiety Rating Scale. This emphasizes the anxiolytic, nootropic and antistress activity of the drug due to which it is believed to be relieving the symptoms of GAD. A research paper published by Natreon, Inc. reveals that extracts of *Ashwagandha (Withania somnifera)* have shown potent anti-stress, cortisol lowering, GABAergic, serotonergic and antioxidant properties in animal and human studies. Furthermore, controlled, single site human studies have shown the anxiolytic potential of *Withania Somnifera* extracts.⁸

Ashwagandha (Withania somnifera) has been shown to have GABA mimetic properties (Mehta et al., 1991; Kulkarni et al., 1993); since GABA agonism has been linked to anxiolysis (Stahl, 1998), it is conceivable that *Ashwagandha (Withania somnifera)* contains a constituent that alleviates anxiety by modulating GABA neurotransmission.⁹

It exhibits action on Central Nervous System, Cardiovascular System, Respiratory System, Gastro Intestinal System and Genito Urinary System due to its immunomodulatory action and promoting neuritic regeneration. It has showed tremendous relief in complains like sleep disturbances, restlessness, etc. which may be

due to the tranquilizing and sedative effect of the drug. *Withania somnifera* (*Ashwagandha* (*Withania somnifera*)) is considered to be the pre-eminent adaptogen.¹⁰ In situations of experimental physical stress in animals, it has shown anti-stress and anabolic activity.¹¹ *Ashwagandha* (*Withania somnifera*) is the drug of choice in symptoms like Anxious mood, Fears, Insomnia, Respiratory symptoms, Genito-urinary symptoms and Autonomic symptoms in the patients of GAD.¹²

On the other hand placebo has also exhibited a fairly good result in managing the disease which supports the fact that a connection indeed exists between the placebo effect and anxiety. In looking at anxiety, depression, manic and bipolar disorders, no specific biochemical changes have been found as a consequence of placebo action. Studies have indicated several areas that could account for placebo effects which may involve changes in autonomic functioning in the central nervous system, immune system changes, endocrine changes, cognitive effects, classical conditioning, and especially expectations due to environment.¹³ GAD is a disease where emotional aspect has been given an equal weightage to the biological aspect. It may help in relieving the condition because of patient's faith in its powers. One cannot be sure of the direction of causality, but placebos, like actual medications, have been shown to act as anxiolytics. There is no certainty about how placebos might act to reduce anxiety, but what is certain is that if placebos act on serotonergic systems to reduce anxiety, then it is the power of suggestibility that has its effects in relieving this disorder.

On the whole despite having insignificant statistical difference in both the groups, Group A, *Ashwagandha* (*Withania somnifera*) granules, showed a better percentage improvement than Group B (Placebo). *Ashwagandha* (*Withania somnifera*) granules have shown superior results in the management of GAD as compared to Placebo granules. Hence, the alternate hypothesis is accepted i.e. *Ashwagandha* (*Withania somnifera*) is effective in the management of Generalized Anxiety Disorder. Any adverse drug reaction (ADR) was not reported during the course of treatment.

ACKNOWLEDGEMENT

The authors would like to thank Dr. M. S. Baghel, Director I.P.G.T. &RA for his valuable support and always encouraging and inspiring Ayurvedic research scholars to pursue authentic research and publishing their research works. A sincere thought of gratitude to Dr. P. K. Prajapati who actively participated in preparation and blinding of the research drugs.

REFERENCES

- 1) Hoffman DL, Dukes EM, Wittchen HU. Human and economic burden of generalized anxiety disorder cited in PubMed - indexed for MEDLINE (PMID: 17146763) cited in 2008; 25(1):72-90. Available online from <http://www.ncbi.nlm.nih.gov/pubmed>
- 2) Tomoharu Kuboyama, Chihiro Tohda and Katsuko Komatsu et al .Neuritic regeneration and synaptic reconstruction induced by Withanolide-A. British Journal of Pharmacology cited in April 2005; 144(7): 961–971. Published online February 14 2005. doi: 10.1038/sj.bjp. 0706122. Available online from: <http://www.ncbi.nlm.nih.gov/pmc/articles/>

- 3) Ghosal S, Lal J, Srivastava R, Bhattacharya S.K, Upadhyay S.N, *et al.* Immunomodulatory and CNS effects of Siterosides IX and X, Two new Glycowithanolides from *Withania somnifera*"; *Phytotherapy Research*, 1989; 3(5) : 201-6
- 4) Bhattacharya S.K, Goel R.K, Kaur R, Ghosal S, *et al.* Anti-stress activity of Siterosides VII and VIII, new Acylsterylglucosides from *Withania somnifera*"; *Phytotherapy Research*, 1987, 1(1) :32-7.)
- 5) Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal *et al.* Anxiolytic activity of Glycowithanolides from *Withania somnifera*. *Phytomedicine: International journal of phytotherapy and phytopharmacology* cited in December 2000; 7(6):463-9. Available online from <http://www.ncbi.nlm.nih.gov/pubmed>
- 6) Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision. Washington, DC, American Psychiatric Association, 2000, pg.476.
- 7) Ermis Reprinted with Psion from M Hamilton: The assessment of anxiety states by rating. *Br J Med Psychol* 32:50, 1959.
- 8) Natreon, Inc. A Clinical Trial to Study the Effects of Sensoril for Patients with Generalized Anxiety Disorder. Published by Clinical Trials. gov: Identifier: NCT01311180, March 2012. Available online from <http://clinicaltrials.gov/ct2/show/NCT01311180#wrapper>
- 9) Chittaranjan Andrade, Anitha Aswath, S.K. Chaturvedi, M. Srinivasa and R. Raguram *et al.* A Double-Blind, Placebo-Controlled Evaluation Of The Anxiolytic Efficacy Of An Ethanolic Extract Of *Withania Somnifera*, *Indian Journal Of Psychiatry*, 2000, 42 (3), 295-301
- 10) Elsakka M, Pavelescu M, Grigorescu E *et al.* *Withania somnifera*, a plant with a great therapeutical future. *Rev Med Chir Soc Med Nat Iasi* 1989 Apr-Jun;93(2):349-50. Available online from <http://www.ncbi.nlm.nih.gov/pubmed/2814052>
- 11) Grandhi A, Mujumdar A.M, Patwardhan B *et al.* A comparative pharmacological investigation of *Ashwagandha (Withania somnifera)* and ginseng. *J Ethnopharmacol* 1994; 44:131-5.
- 12) Sethi *et al.* Comparative evaluation of Medhya effects of *Ashwagandha (Withania somnifera)* & Shatavari in the management of Generalized Anxiety Disorder (GAD), M.D.Thesis, 2007, Tilak Ayurved Mahavidyalaya, Pune (M.S.), MUHS.
- 13) Straus J L, Cavanaugh S A *et al.* Placebo Effects: Issues for clinical practice in psychiatry and Medicine. *Psychosomatics* 1996 Jul-Aug;37(4):315-26. Available online from: <http://www.ncbi.nlm.nih.gov/pubmed>

CORRESPONDING AUTHOR

Dr. Khyati.S.Sud
501, Shiva Residency, Rajputpara-3,
Limda Lane, Jamnagar-361001, Gujarat
Email: drkhyatisud@gmail.com

Source of support: Nil

Conflict of interest: None Declared