A DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION OF THE ANXIOLYTIC EFFICACY OF AN ETHANOLIC EXTRACT OF WITHANIA SOMNIFERA

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ABSTRACT

A double-blind, placebo-controlled study was conducted to evaluate the efficacy an ethanolic extract of Aswagandha (Withania somnifera), in patients with ICD-10 anxiety disorders. The sample comprised 39 subjects, of whom 20 received the drug and 19 received placebo. The two groups were sociodemographically and clinically similar at baseline. At 2 and 6 weeks follow-up, data from approximately 85% of patients in each group were available for analysis. Statistical trends favouring the drug were observed at both time points. At 6 weeks, significantly more patients met a priori response criteria in the drug group (88.2%) as compared with the placebo group (50%). The drug was well-tolerated and did not occasion more adverse effects than did placebo. It is concluded that this ethanolic extract of Withania somnifera has useful anxiolytic potential and merits further investigation.

Key words : Anxiety disorder, generalized anxiety disorder, adjustment disorder with anxiety, panic disorder, Aswagandha, Ayurvedic treatment, herbal therapy, clinical trial

Anxiety disorders are common, and have a lifetime prevalence that exceeds 15% in the general population (Kessler et al.,1994). Conventional anxiolytic treatments include the benzodiazepines, antidepressant drugs in low doses, and buspirone. All these three categories of drugs are associated with disadvantages in the management of anxiety. Benzodiazepines and antidepressant drugs occasion sedation and impaired psychomotor performance; while benzodiazepine therapy results in drug dependence, antidepressant therapy is associated with anticholinergic and/or other adverse effects. Antidepressant drugs and buspirone may both produce initial worsening of anxiety (Andrade,2000). There is therefore a need for the development of anxiolytic therapies that carry fewer disadvantages to the patient.

In India, Aswagandha (Withania somnifera) has been used for centuries in Ayurvedic medical practice to reduce symptoms of anxiety and stress (Iyengar,1981; Handa,1995; Satyavati,1995). In laboratories in the USA, Withania somnifera extracts have been shown to possess high affinity for GABA receptors (Cott et al.,1994). The experimental drug is an ethanolic extract of Withania somnifera. In Indian research, this extract has been shown to have GABA-mimetic properties (Mehta et al.,1991; Kulkarni et al.,1993), which might conceivably mediate its demonstrated anticonvulsant (Kulkarni et al.,1993; Kulkarni & George,1996) and antikindling (Kulkarni et al., 1994) actions. Since GABA agonism has been linked to anxiolysis (Stahl,1998), these findings support the recommendation in Ayurveda that Aswagandha be used for tranquillization. Extracts of Aswagandha may therefore be useful

in anxiety disorders that present in psychiatric practice.

In an unpublished open clinical trial (data on file; available upon request from manufacturer), Dave at the Rasiklal Shah Sarvajanik Hospital, Gujarat, studied the efficacy and safety of ethnolic extract of Aswagandha 250 mg twice daily in 50 patients with anxiety disorders. By the end of the first month of treatment, 36 (72%) of patients showed moderate to excellent improvement; in about half of these cases, benefits were observed within the first fortnight. These 36 patients were continued on the drug for a maximum of 18 months, during which period the medication was withdrawn under psychotherapeutic support. It was observed that the drug satisfactorily attenuated anxiety symptoms and did not occasion any adverse effects of note.

In view of the encouraging laboratory and clinical results, a double-blind, placebo-controlled, dose-ranging study was designed to assess the anxiolytic efficacy and adverse effects of this ethanolic extract of Aswagandha.

MATERIAL AND METHOD

The sample comprised consecutive patients diagnosed with ICD-10 generalized anxiety disorder, mixed anxiety and depression, panic disorder, and adjustment disorder with anxiety. The sample was recruited from two clinical units in a large mental hospital setup, and from a private psychiatric hospital, both located in urban India. The study was conducted on an outpatient basis.

Patients were recruited only if their treating consultant considered them to be sufficiently symptomatic to warrant further pharmacotherapeutic intervention. Further selection criteria included an absence of significant past or current history of cigarette smoking, drug or alcohol abuse, or medical or psychiatric illness that may have prejudiced the diagnosis or ratings of anxiety, or the response to anxiolytic medication. Informed consent was obtained in writing from recruited patients. The project protocol received the approval of the Ethics Committee in the institution of the first author.

Patients were randomized to receive either ethnolic extract of Aswagandha (250 mg/tablet) or placebo, administered as identical tablets in the dose of 2 tablets twice a day. The first follow-up was conducted after 2 weeks, at which time a decision was taken to lower or raise the dose based upon the clinical response and the adverse effects reported. Subsequently, dose titrations to individual requirements were allowed at weekly intervals, subject to a minimum of 2 and a maximum of 10 tablets per day. For ethical reasons, existing medications (if any) were continued unchanged throughout the course of the study. No other medication, or any other form of therapeutic intervention, was prescribed during the study.

Patients were assessed at baseline, at week 2, and at week 6 (the treatment endpoint) using the following instruments :
1. Hamilton Anxiety Scale (Bech et al.,1986); assessed by the rater only.
2. Global Rating Scale; assessed separately by patient and rater. This instrument had rating points anchored as follows : 0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms; 4=very severe symptoms. Decimal ratings were encouraged.
3. Systematic assessment for treatment emergent effects (SAFTEE) symptom checklist (Levine & Schooler,1986), assessed by the rater only, and at weeks 2 and 6 only.

Patients and raters were alike blind to the treatment allocation until after the study endpoint.

Statistical analysis : Baseline data were analyzed for all recruited patients. Efficacy and adverse effects data were analyzed only for those patients who provided follow-up assessments at week 2 and beyond. The last observation carried forward (LOCF) method was employed for all patients who completed the first-fortnight assessment but who dropped out subsequently. Response was defined a priori as a reduction in Hamilton

Anxiety score to 12 or below, associated with a global rating from both patient and rater of not more than 1 (mild symptoms).

Proportions were compared between groups using the X^2 test (with Yates continuity correction for 2x2 contigency tables), or the Fisher's exact 2-tail probability test when the requirements for X^2 testing were not met. Means were compared between groups using the independent sample student's 't' test, with modified degrees of freedom wherever indicated to correct for heterogeneity of variances as determined by the Fmax test. When distributions were non-normal, mean ranks between groups were compared using the Mann-Whitney U test with z corrected for ties. Means were compared between groups and across time using repeated measures multivariate analysis of variance (RMANOVA); Pillai's trace was selected as the test criterion.

RESULTS

The sample comprised 39 subjects, of whom 20 received the experimental drug and 19 received placebo. The sample was 61.5% male, and the mean (standard deviation) [M (SD)] age of the sample was 41.3 (13.8) years. The sociodemographic and clinical variables of the sample are presented in tables 1-3. There were no significant differences between experimental drug and placebo groups at baseline.

At the end of week 2, when the first follow-up assessments were due, 3 patients belonging to each group dropped out of the study, and attempts to trace them to ascertain the reasons for drop out failed. These 6 patients could not

TABLE 1
AGE AND SEX DISTRIBUTION IN DRUG
(N=20) AND PLACEBO (N=19) GROUPS*

Variable	Drug group	Placebo
Age (in yrs.) Range	18-68	18-69
(Mean S.D.)	41.9 (14.4)	40.7 (13.4)
	t=0.27, d.f.=37, NS	
Sex : Male 13	11	
Female	7	8

X^2=0.02, d.f.=1, NS (with yates correction)

TABLE 2
DIAGNOSTIC BREAKUP OF DRUG (N=20)
AND PLACEBO (N=19) GROUPS

Diagnosis	Drug group	Placebo
Generalized anxiety disorder	13	11
Mixed anxiety and depresssion	3	5
Adjustment disorder with anxiety	2	1
Panic disorder	2	2

TABLE 3
BASELINE CLINICAL DESCRIPTION OF DRUG
(N=20) AND PLACEBO (N=19) GROUPS*

Variable	Drug group	Placebo	Significance#
Duration of illness (years)	0.5-40 7.4 (10.3)	0.2-20 6.4 (6.3)	z=0.21, NS
Hamilton Anxiety score	15-28 17.3 (6.4)	15-28 18.6 (4.5)	t=0.72, d.f.=37 NS
Global rating (patient)	1-4 2.6 (0.8)	2-4 2.8 (0.5)	t=1.10, d.f.=31.6, NS
Global rating (rater)	1-4 2.5 (0.9)	1-4 2.8 (0.6)	t=0.98, d.f.=37, NS

* data presented are range, mean and standard deviation.
# Mann-Whitney U test with z corrected for ties, and independent sample Student's 't' test with modified d.f., whereve indicated, to correct for heterogeneity of variances.

be assessed on any measure at week 2. At week 6, a further 6 experimental drug patients and 7 placebo patients withdrew from the study. Reasons for withdrawal are presented in table 4. There were no significant differences between groups in individual reasons for withdrawal.

At baseline, according to the protocol, all

TABLE 4
REASONS FOR DROP OUT IN DRUG (N=20)
AND PLACEBO (N=19) GROUPS

Reason for drop out	Drug group	Placebo
Lack of benefit	3	3
Adverse effects	2	3
Other*	1	1
Unknown**	3	3

* These patients developed a crisis in their personal environments, which necessitated more intensive medication.
** These patients dropped out before the first follow-up; all other patients completed at least one follow-up.

patients were advised to take two tablets twice daily. At week 2, based on initial response, patients were advised 2-6 tablets/day with a M(SD) of 4.5 (1.1) tablets in the drug group, and 2-6 tablets/day with a M(SD) of 4.3 (1.5) tablets in the placebo group. The difference between groups was not significant (t=0.57, d.f.=31, NS). At week 6, the patients were receiving 2-9 tablets/day with a M(SD) of 5.0 (2.1) tablets in the drug group, and 2-8 tablets/day with a M(SD) of 4.7 (2.0) tablets in the placebo group. The difference between groups was again not significant (t=0.40, d.f.=21, NS).

Efficacy and adverse effect data were available for 17 of the 20 experimental drug patients (85%) and for 16 of the 19 placebo patients (84.2%). At the second week, 12 of 17 experimental drug patients (70.6%) met criteria for response, while 6 of 16 placebo patients (37.5%) were similarly classified; the difference was however not statistically significant (X^2=2.43, d.f.=1, NS). At the sixth week, 15 of 17 drug patients (88.2%) met criteria for response, while 8 of 16 placebo patients (50%) were similarly classified; the difference was statistically

significant (Fisher's exact two-tailed probability=0.026).

A quantitative examination of anxiety scores across time (Table 5) showed that both groups improved significantly (Pillai's trace=0.68, F=32.13, d.f.=2,30, p<0.001) from week 2 itself. There was a main effect for drug that approached significance (F=3.35, d.f.=1,31, p=0.077). Independent comparisons at week 2 (t=1.70, d.f.=31, p=0.098) and week 6 (t=1.94, d.f.=31, p=0.062) revealed statistical trends that favoured the experimental drug.

A quantitative examination of changes in global scores across time (Table 6) showed significant improvements for both patient (Pillai's trace=0.73, F=40.56, d.f.=2,30, p<0.001) and rater-assessed (Pillai's trace=0.66, F=29.60, d.f.=2,30, p<0.001) functioning from week 2 itself. No significant advantage for experimental drug was however obtained in either the former (Pillai's trace=0.02, F=0.25, d.f.=2,30, NS) or the latter (Pillai's trace=0.02, F=0.31, d.f.=2,30, NS) assessments. Independent testing at each of weeks 2 and 6 again did not demonstrate an advantage for experimental drug.

A quantitative analysis of adverse effects (Table 7) showed that 15 experimental drug treated patients reported a M(SD) of 1.2 (1.2) adverse effects at week 2, and 8 patients reported a M(SD) of 0.25 (0.5) adverse effects at week 6. Corresponding data for placebo-treated patients were 0.9 (1.1) from 15 patients at week 2, and 0.67 (1.1) from 9 patients at week 6. The difference between groups was not significant either at week 2 (Mann-Whitney; z=0.80, NS) or at week 6 (Mann-Whitney,

TABLE 5
RANGE, M(SD) CHANGE IN HAMILTON ANXIETY SCORES ACROSS TIME IN DRUG (N=17) AND PLACEBO (N=16) GROUPS

	Week 2	Week 6
Drug	5-22	0-22
	11.0 (4.7)	8.5 (5.3)
Placebo	4-25	4-25
	14.1 (5.6)	12.2 (5.6)

* baseline data have been presented in Table 3.
# statistical trends favoured the drug group at both week 2 and week 6.

TABLE 6
RANGE, M(SD) GLOBAL ASSESSMENTS OBTAINED FROM PATIENTS AND RATER AT WEEK 2 AND 6 IN DRUG (N=17) AND PLACEBO (N=16) GROUPS ##

	Patients' assessment		Rater's assessment	
	Week 2	Week 6	Week 2	Week 6
Drug	0.5-3	0-3	0.5-3	0-3
	1.9 (0.8)	1.4 (0.9)	1.8 (0.7)	1.4 (0.9)
Placebo	0.5-3.5	0-3.5	0.5-3	0.5-3
	2.2 (1.0)	1.8 (1.0)	2.0 (0.9)	1.8 (0.8)

* baseline data have been presented in Table 3.
# there were no differences between drug and placebo groups at either week 2 or week 6.

TABLE 7
FREQUENCY OF EXPERIENCE OF ADVERSE
EFFECTS AT WEEKS 2 AND 6

	Number of advers effects reported			
	none	1	2	3
At week 2				
Drug group	6	3	3	3
Placebo group	6	2	4	1
At week 6				
Drug group	6	2	0	0
Placebo group	6	1	1	1

z=0.60, NS).

A qualitative analysis of adverse effects is presented in table 8. With the possible exception of greater drowsiness, heaviness of head and related symptoms with Aswagandha (during the initial few days only), there were no differences between groups in the nature and frequency of individual adverse effects. The treatments were in general well-tolerated, with

TABLE 8
ADVERSE EFFECTS REPORTED BY DRUG (N=17)
AND PLACEBO (N=16) PLANTS

Adevrse effect	Drug group	Placebo group
Giddiness	0	2
Drowsiness	2	0
Dullness	0	1
Heaviness of head	4	1
Increased frequency of migraine	1	0
Fatigue	1	1
Withdrawal fatigue	1	0
Chest pain	0	1
Chest infection	0	1
Itching	1	0
Burning eyes	0	1
Burning urine	0	1
Numb hands	1	0
Multiple somatic complaints	0	1
Heat in body	0	1
Bitter taste	1	0
Decreased appetite	1	0
Increased appetite	1	1
Decreased sleep	2	0
Gastritis	2	1
Heaviness in stomach	1	1
Diarrhoea	0	1
Menstrual irregularities	0	2
Worsening of obsessive-compulsive disorder	0	1

* Data presented are number of patients reporteing each adverse effect.

most adverse effects being mild in severity, appearing early during therapy, and manageable by adjustment in dose; however, there were 5 dropouts due to adverse effects : two in the Aswagandha group (reasons : increased gastric acidity; withdrawal fatigue), and three in the placebo group (reasons : slowness and dullness; giddiness, weakness and fatigue; burning of eyes, burning while passing urine, and worsening of obsessive-compulsive symptoms).

Most patients experienced the adverse effects early during the study (Table 7). At the study endpoint, the drugs were withdrawn abruptly. While no formal assessments of withdrawal were conducted, clinical records of these patients documented no withdrawal phenomena in either group.

DISCUSSION

India has a rich tradition in herbal medicine, and it is unfortunate that little work is being conducted by allopathic neuroscientists to identify elements in the herbal pharmacopoeia that might be of use in psychiatric disorders. The western pharmaceutical industry is already involved in the research of medicinal plants, and it would be doubly unfortunate if western scientists patent molecules of psychotropic value, that have been derived from Indian herbs. This subject has been discussed in greater detail elsewhere (Andrade et al.,1998). The present study was therefore a trail blazer in the field of anxiety disorders.

Essentially, this study demonstrated a trend for the anxiolytic superiority of drug over placebo at week 2, and a statistically significant superiority at week 6. The advantage for Aswagandha was observed only with Hamilton Anxiety ratings, and with responder analyses, but not with global ratings; this may have been because the latter had a narrower rating range, and were therefore less sensitive to clinical change. Aswagandha was well tolerated, with adverse effects being comparable to those observed with placebo. At 6 weeks, abrupt withdrawal did not appear to be associated with

any withdrawal phenomena. Thus, Aswagandha appeared to have several of the advantages but none of the disadvantages of conventional anxiolytic drugs such as the benzodiazepines, the tricyclic antidepressants, and buspirone. This study therefore confirmed the preliminary observations of the unpublished open study of the experimental drug in patients with anxiety disorders (Manufacturer, data on file).

Benzodiazepines produce anxiolysis within days; antidepressant drugs and buspirone reduce anxiety in approximately a fortnight. Speed of response was regrettably not addressed in this study. However, it is likely that significant response will be obtained in most patients within the first fortnight of therepy itself, as Aswagandha was near-significantly superior to placebo at this time point. Future studies need to address the magnitude of anxiolysis during the first week to ascertain the position of Aswagandha relative to conventional anxiolytic drugs.

What might be the mechanism of action of Aswagandha? As reviewed earlier, Aswagandha 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 Aswagandha contains a constituent that alleviates anxiety by modulating GABA neurotransmission.

The high placebo response rate (50%) was interesting; however, such high placebo response rates are well-known with anxiety disorders. Studies on patients with panic disorder, for example, have demonstrated placebo-response rates in the range of 40 to 50% (Schweizer et al.,1993; Londborg et al.,1998).

This study had a few limitations. The sample size was relatively small, which might have been the reason why certain obvious statistical trends escaped significance. The inclusion of multiple diagnoses precluded an identification of the value of Aswagandha in each; samples for individual diagnoses were too small to permit subgroup analyses.

It is concluded that further investigation of the anxiolytic properties of Withania somnifera

are warranted, with particular reference to ethanolic extracts. Comparisons with convetional anxiolytic drugs are necessary. The relevance of the GABAergic properties of the extract to anxiolysis also require investigation. Long-term studies with structured withdrawal programmes should be conducted to document the long-term efficacy, safety, and dependence vs withdrawal profile of the treatment. Finally, attemts need to be made to identify the specific therapeutic element contained in the extract.

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