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A CLINICAL STUDY TO COMPARE THE EFFICACY OF PAROXETINE VERSUS ASHWAGANDHA IN PATIENTS SUFFERING FROM GENERALIZED ANXIETY DISORDER.

Pharmacology

KEYWORDS: GAD, Ashwagangha, Paroxetine, HAM A, HADS

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ABSTRACT

Anxiety disorders have a lifetime prevalence which exceeds 15% in the general population and particularly Generalized Anxiety Disorder (GAD) (lifetime prevalence of 5.1%) accounts for second most frequent psychiatric disorder in the primary care setting. METHODOLOGY The present 12 weeks' study was a prospective, randomized clinical study in 60 subjects. The aim of the study is to compare the efficacy between two drugs using HAM-A, HADS, CGI scales. **Results:** In Paroxetine group there was only very little clinical difference in HAM-A and HADS reduction than Ashwagandha group however the difference did not reach statistical significance. Similarly, reduction in CGI scores did not reach statistical significance. C**onclusion:** Ashwagandha (Withania Somnifera) when compared was as much efficacious as Paroxetine but had better side effect profile hence could be given in patients not tolerating the side effect of Selective serotonin reuptake inhibitors (SSRIs) or can be given in mild to moderate anxiety as an initial drug.

INTRODUCTION

Anxiety disorders have a lifetime prevalence which exceeds 15% in the general population for which treatments include the SSRIs, SNRIs, benzodiazepines, buspirone , etc. [1] (*Kessler et al., 1994*) Benzodiazepines and antidepressant drugs cause wide range of side effects like sedation , impaired psychomotor performance, drug dependence, anticholinergic, autonomic side effects, and some antidepressant drugs and buspirone may both produce initial worsening of anxiety (*Andrade,2000*).[2] Another ayurvedic anxiolytic *Ashwagandha (Withania somnifera)* studied in psychiatry and ayurveda is used as a *Rasayana* (Rejuvenation therapy) which helps in Neuritic regeneration and synaptic reconstruction. This herb is having Immunomodulatory anti-fatigue and anti-stress activity.[3-7] *Andrade et al. 1998* concluded in placebo controlled double blind study that ashwagandha had anxiolytic effect and had adverse effects comparable to placebo. Generalized anxiety disorder a common anxiety disorder with a lifetime prevalence of 5.1% , is the second most frequent psychiatric disorder in the primary care setting as per WHO sponsored multi-centric clinical trial , with approximately 8% of patients suffering from this illness. The course of generalized anxiety disorder tends to be chronic and recurrent.[7-11] Paroxetine ,SSRI when compared to imipramine and 2 -chlordesmethyl-diazepam (not available in the United States) found antidepressants were more effective than the benzodiazepine in alleviating psychic symptoms of anxiety rather than the somatic symptoms and also showed efficacy in the treatment of other anxiety disorders.[12-14] In the present study established anxiolytics one from modern medicine Paroxetine and another from ayurvedic medicine Ashwagandha was compared in 60 subjects with respect to efficacy and safety.

AIMS AND OBJECTIVES

The primary outcome measures were to observe mean change from baseline in anxiety subset of Hospital Anxiety and Depression Scale (HADS) and Hamilton Anxiety Scale (HAM-A) to compare efficacy between Paroxetine and Ashwagandha.[15-16]

METHODOLOGY

The present study was a prospective, randomized clinical study. Patients with generalized anxiety disorder (GAD) were randomized (1:1) to Paroxetine and Ashwagandha two treatment groups. The study was carried out in outdoor patients in the department of Psychiatry, T.S. Misra Medical College and Hospital Lucknow after obtaining written informed consent from patients who were included in the study. Psychiatrist had enrolled participants, administered scales and assessed the clinical outcomes. Side effect monitoring was done and by a pharmacologist and a psychiatrist using clinical improvement was assessed by Clinical Global Impression (CGI). The study was conducted from September 2016 to January 2017.

INCLUSION CRITERIA

The subjects were male and female outpatients, 18 years and older, who fulfilled Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for generalized anxiety disorder as determined by psychiatric evaluation, score of at least 20 on the Hamilton Rating Scale for Anxiety was required, including a score of 2 or more on items 1 (anxious mood) and 2 (tension).

EXCLUSION CRITERIA

Patients having Axis I or Axis II disorder other than GAD disorder, scoring > 4 on MARDS [20] items number 10 (suicidal thoughts) and total score of >17 at screening or baseline, history of non response to an adequate (6 week) trial of three or more antidepressant (with or without mood stabilizers) during the current episode, with imminent risk of suicide or injury to self, others, or property, pregnant, lactating women or women not using medically accepted method of contraception, subjects with human immunodeficiency virus (HIV) seropositivity (or history of seropositivity), history of malignancy, or any chronic incapacitating illness were excluded.

Patients were followed per 2 weeks at the Psychiatry OPD T.S.M. Medical College and hospital. At each visit, HAM-A, HADS, CGI were applied, review of anxiety and comorbid symptoms was done side effects were either elicited observed or recorded by using DOTES scale. The functional impairment was assessed at the initial part of the study and than during the completion of the study. This study consisted of two periods: a prospective baseline screening period lasting up to 2 weeks (week -2 to week 0, T0 with T signifying 2 weeks), and a treatment period lasting 12 weeks after enrollment (weeks 0-12, T1-T6). The treatment phase consisted of a 2-week titration period (T1) and a 10-week maintenance period (T2-T6). In the first group during the titration period, subjects were given 12.5 mg/day paroxetine once daily in the first week, followed by 25mg/day paroxetine in divided doses (twice daily) in the second week. In the second group during the titration period, subjects were given Ashwagandha 2gm/day in divided doses in the first week, followed by 4gm/day in divided doses. All the patients were advised to follow *Pathyapathya* schedule (avoidance of aetioiogical factor). Regulated diet (three meals and three snacks providing adequate calories and meals devoid of nicotine, caffeine, reheated food, aerated drink), and lifestyle modification included minimum 8 h sleep, moderate exercise such as morning or evening walk for 30-60 min and abstention from smoking/drinking was advocated in third group.

A detailed baseline assessment was done as per the semi structured proforma which included psychiatric and medical history, physical examination and detailed mental status assessment. Baseline investigations (Haemoglobin, TLC, DLC, ESR, Blood Sugar, Liver Function Tests and Blood Urea) were carried out.

Instruments & Medications used were

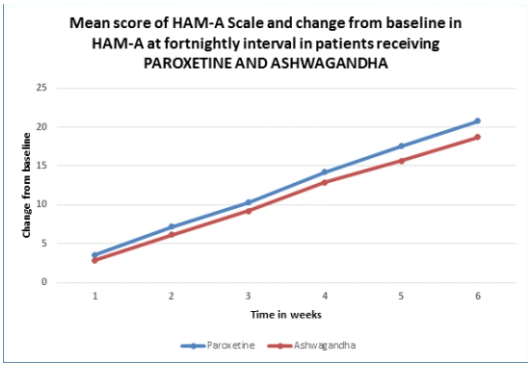
Paroxetine was procured Xet –Cr 12.5mg and 25mg tablet (Zydus Cadila Healthcare)

Ashwagandha was procure from Organic India Ashwagandha capsule (400mg capsules).

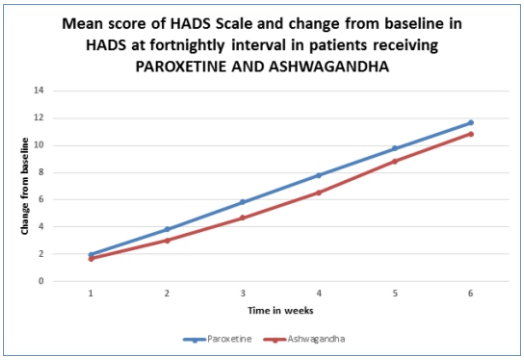
- Semistuctured proforma for socio demographic details.
- Details of psychiatric history and examination
- Hamilton Anxiety Scale (HAM-A)
- Hospital Anxiety Depression Scale (HADS)
- Independent t-test was applied for changes in scores from baseline in both groups. P value <0.05 was considered significant.

RESULTS

175 subjects were initially screened of which 55 subjects were excluded. Out of the 120 subjects who were taken in the study 17 subjects dropped in group Paroxetine as compared to 3 in group Ashwagandha. Regarding socio demographic variables there were no significant differences between the two groups, in general females were more effected. There was likelihood of illness in patients having family history of similar illness. Onset of illness was a bit more in age group of more than 30 years of age and duration of illness was about 10 years. Scores were taken and independent t-test was applied in each pair of scores. P value <0.05 was considered significant for the difference in their scores.



In Paroxetine group there was only very little clinical difference in HAM-A reduction than Ashwagandha group however the difference did not reach statistical significance. Comparing from baseline there was significant difference in anxiety scores in either of the groups. On an average anxiety and tension item of HAM-A there was scoring of 3.2 & 2.8 in Group A and 3.1 & 2.9 in Group B. There was reduction HAM- A Scores at the completion of 12 weeks in either of the groups with more in Group A as compared to Group B.



In Paroxetine group there was clinically more reduction of HADS score as compared to Ashwagandha group and in either of the groups there was significant difference in the scores from the baseline scores (p value >0.05). However, the difference between the groups did not reach any statistical significance.

Table - Change in CGI Score from Baseline

Change from baseline		PAROXETINE (n = 30)			ASHWAGANDHA (n = 30)		
		Same	Decrease	Increase	Same	Decrease	Increase
After2weeks	N	18	10	02	19	09	02
	%	59.4	33	06.6	62.7	29.7	6.6
After4weeks	N	16	11	.3	17	10	03
	%	52.8	36.3	9.9	56.1	33	9.9
After6weeks	N	15	13	02	14	13	03
	%	49.5	42.9	6.6	42.2	42.9	9.9
After8weeks	N	13	16	01	14	15	01
	%	42.9	52.8	3.3	46.2	49.5	3.3
After10weeks	N	10	20	00	11	19	00
	%	33	67	00	36.3	62.7	00
After12weeks	N	08	22	00	09	21	00
	%	26.4	73.6	00	29.7	71.3	00

Overall there was more reduction in CGI scores in PAROXETINE group as compared to ASHWAGANDHA at the end of 12 weeks but there was no statistical significance between the two groups in terms of improvement from the baseline.

Discussion

The west is tirelessly working to prove what is written in ancient Indian treatise of medicine, philosophy and spiritualism and what more shameful it would be that westerners employing the latest tools of evidence based medicine prove that herbs enlisted in ancient texts are having anxiolytic and antidepressant properties which also has been discussed by *Andrade et al.,1998* [21]. There were studies done in the past which have compared paroxetine and Ashwagandha in the past.[3-4 ,12-14.] In the present study of 12 weeks comprising of 60subjects there was comparison between established anxiolytic SSRI Paroxetine along with ayurvedic medicine Ashwagandha. There was only slight better rating of HAM-A, HADS, CGI in subjects of Paroxetine group however there were less drop outs and better tolerability in Ashwagandha group. The earlier studies of Withania Somnifera with placebo have already proved its anxiolytic effect [3-4]. Owing to the side effects of SSRI and wide spread promotion of ayurveda in the current scenario Ashwagandha can be a choice in treating patients with GAD. Its nature use indications have been mentioned in ayurvedic text. Its pharmacodynamics when studied in west showed that it possess high affinity for GABA receptors (*Cott et al.,1994*) and when studied in India it was deducted that it is having GABA-mimetic and anti-kindling properties (*Mehta et al .1991; Kulkarni et al.,1993*), which might conceivably mediate its tranquilizing, anti-stress, anti-fatigue and other properties.[22-27.] It exhibits action on Central Nervous System, Cardiovascular System, Respiratory System, Gastro Intestinal System and Genito-Urinary System due to its immune modulatory action and promoting neuritic regeneration. It has showed tremendous relief in complains like sleep disturbances, restlessness, etc.

Conclusion

This study proves anxiolytic property of Withania Somnifera when compared with Paroxetine though was less efficacious but had better side effect profile , hence can be given in patients not tolerating the side effect of SSRIs or can be given in mild to moderate anxiety as a initial drug.

Limitations

The present study had small sample size and limited duration. The authors recommendations are to do multi-centric RCTs with large sample size to prove the same and parallel trying to explore its pharmacodynamics and pharmacokinetics properties so that its active ingredient can be applied in present day world.

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