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OPIPRAMOL VERSUS ESCITALOPRAM IN THE TREATMENT OF GENERALIZED ANXIETY DISORDER

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ABSTRACT

Objective: To compare the efficacy of opipramol and escitalopram in the treatment of generalized anxiety disorder. **Materials and Methods:** The study was conducted in outpatients (18 to 65 years old) of psychiatry department, diagnosed with Generalized Anxiety disorder (GAD) according to DSM-IV criteria. Total of 96 patients were included in the study with 50 patients receiving opipramol 50mg once daily and 46 escitalopram 5mg. The efficacy was assessed using Hamilton Anxiety Rating Scale (HAM-A) at the baseline and after 4 weeks. Paired t-test was used to assess difference between before and after treatment within the groups. To assess difference between the groups unpaired T-test was used. p value of <0.05 or less was considered for statistical significance. **Results:** Mean changes in HAM-A scores from baseline to 4 weeks within group for opipramol and escitalopram was highly significant ($p < .000$). Between opipramol and escitalopram treated group there was no significant difference in mean total HAM-A scores (p .85). All the adverse events in both the group were mild to moderate. **Conclusion:** Opipramol is effective in the treatment of GAD and it is as effective as escitalopram.

KEYWORDS: Opipramol, esitalopram, Generalized anxiety disorder, HAM-A.

INTRODUCTION

Generalized anxiety disorder (GAD) is characterized by excessive, pervasive and uncontrollable worry that causes debilitating psychic and somatic symptoms, including irritability, restlessness, concentration difficulties, clammy hands, dry mouth, sweating, nausea and diarrhea.[1] The lifetime prevalence of GAD varies, but studies suggest that it is about 5-6%.[2] An epidemiological study suggests that the prevalence of GAD in Indian population was found to be 5.8%.[3] GAD is a chronic disorder with a gradual onset and it is generally recurrent, which is unlikely to remit spontaneously.[4] Untreated GAD produces significant impairment in daily functioning and quality of life.

Benzodiazepines have been widely used in the management of anxiety disorders. They have rapid onset of action and are effective in anxiety but their usefulness is limited, withdrawal is associated with distressing symptoms on long term use.[5] Buspirone is less likely to cause withdrawal symptoms, however its use in clinical practice is limited because of late onset of action and multiple daily doses.[6] Tricyclic antidepressant drug imipramine is effective in the treatment of GAD, but their side effects including anticholinergic adverse effect profile can limit overall patient compliance. Selective serotonin reuptake inhibitors (SSRIs) are well tolerated, nonetheless these agents are associated with adverse effects, including somnolence, weight gain, and sexual side effects with increased risk of bleeding.[7,8,9]

Despite the availability of so many effective drugs, there is need for new compound probably acting through different mechanism of action and to overcome the disadvantages of currently available treatment modalities. There is sufficient literature available on sigma receptors in the treatment of various psychiatric disorders. Animal studies and clinical studies have shown the importance of these receptors in the treatment of anxiety, depression, bipolar disorder and schizophrenia.[10] Hence sigma receptors can be the target for many psychotropic drugs. Opipramol is a sigma receptor agonist, clinically has been shown to have a broad spectrum of anxiolytic activity.

These properties of sigma receptor agonist led to conduct this efficacy study of opipramol vs escitalopram in generalized anxiety disorder patients.

METHODOLOGY

It is an open label prospective study conducted in the Department of psychiatry, Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka from March 2014 to February 2015 after the approval of protocol from the institutional ethical review board. The study was conducted in accordance to the protocol after written informed consent from study subjects.

Study Endpoints

- Study primary endpoint was to assess the efficacy of opipramol and escitalopram in the treatment of GAD.
- Secondary study endpoint was to assess the tolerability of opipramol and escitalopram.

Subject Selection

A. Inclusion criteria

1. Patients diagnosed with Generalised anxiety disorder (GAD).
2. Aged between 18years and 65years.
3. Both genders.

B. Exclusion Criteria

1. Patients having other Psychiatric disorders.
2. History of suicidal ideation and attempts.
3. History of alcohol and substance abuse/dependence.
4. Treatment with the study drug within 4weeks of entry into the study.
5. Pregnant and Lactating women.

Study Procedure

This study was conducted on patients of generalized anxiety disorder, diagnosed according to DSM-IV criteria. A total of 96 patients were included in the study, 50 patients in opipramol group and 46 patients in escitalopram group. After the diagnosis the patients were started on study drug, tablet opipramol 50mg once daily or escitalopram 5mg once daily and titrated to higher dose if necessary. Throughout the study patients are assessed twice, once during the baseline i.e. at time of enrollment and the other during the week 4 visit. Efficacy of the drug was assessed by using Hamilton anxiety scale (HAM-A) by M Hamilton for GAD. The sociodemographic data and adverse events of drug were recorded in a self-designed proforma.

STATISTICAL ANALYSIS

All the study end point analysis were performed based on per-protocol population. For continuous variable i.e Hamilton anxiety Scale (HAM-A), mean and standard deviation were calculated. Paired t-test was used to assess difference between before and after treatment within the groups. To assess difference between two groups unpaired t-test was used. p value of <0.05 or less was considered for statistical significance. SPSS software version 20 was used for statistical analysis.

RESULTS

Population

Totally 96 patients were included in the study, 50 patients received opipramol 50mg once daily and 46 patients received escitalopram 5mg. 38 patients in opipramol group and 36 in escitalopram group completed study with overall completion rate of 77%.

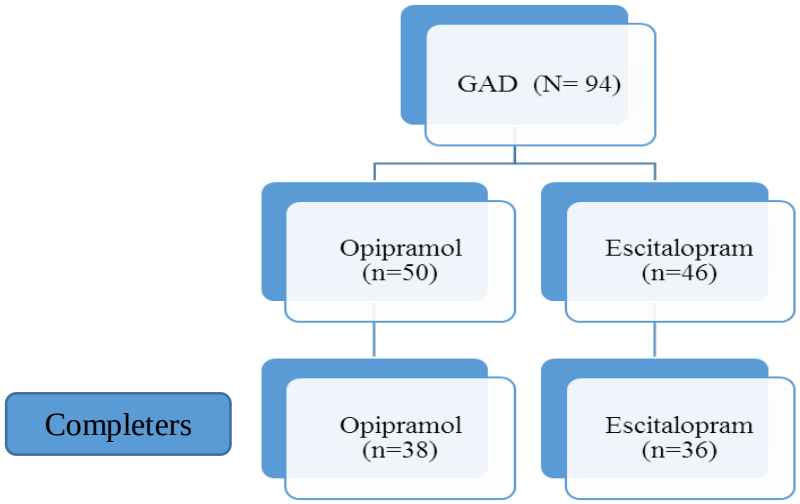

Figure 1. Patients enrolled in the study.

The frequency of age and gender distribution in both the groups were comparable. All the patients in both groups fall within the age of 21 to 50 years and there is no much difference in the frequency of gender distribution but frequency of distribution in females is slightly higher for both the groups.

Efficacy results

Results at end of 4 weeks are presented in Table 1 and 2 for prospectively defined efficacy measure. In opipramol treated group the mean HAM-A scores decreased from 31.6 to 14.4 at the end of the study. The comparative analysis within the opipramol treated group, the changes in the total HAM-A scale scores were highly significant (17.21±4.71, p <0.000). The

mean changes in total HAM-A scores were 31.2 to 14.2 in the escitalopram group and were highly significant within the group (17±4.96, p<0.000). On comparison between opipramol treated group and escitalopram treated group there was no significant change in total HAM-A scores (p 0.85).

Table 1. Comparison of HAM-A score before and after treatment within the groups

Groups		N	Mean	Std. Deviation	paired t test		
					t Value	P Value	Sig
OPI Group	Before	38	31.58	3.87	22.53	P<0.000	HS
	After		14.37	2.67			
EST Group	Before	36	31.17	3.78	20.57	P<0.000	HS
	After		14.17	2.41			
HS = Highly Significant, Sig= Significance							

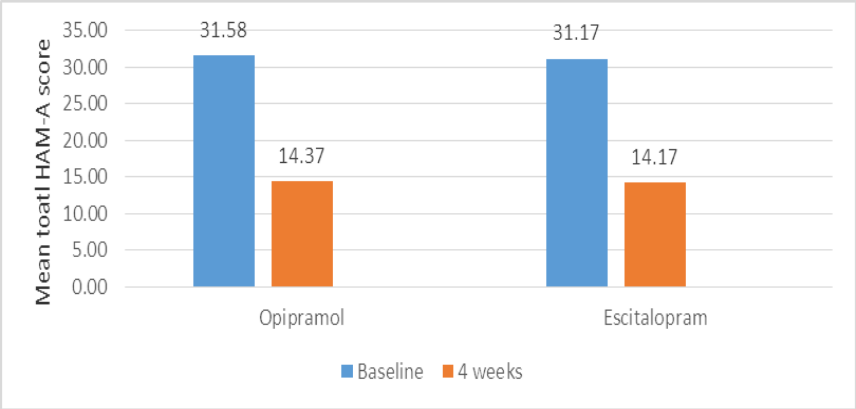

Figure 2. Mean total HAM-A scores.

Table 2. HAM-A total score difference between the groups

groups	N	Mean difference		Unpaired t test		
		Mean	Std. Deviation	t Value	P Value	Sig
OPI Group	38	17.21	4.71	0.18	0.85	NS
EST Group	36	17.00	4.96			

Tolerability

Opipramol treatment group were well tolerated. The most commonly observed adverse events in the opipramol group were fatigue (8%), dryness of mouth (6%) and increased desire for sleep (10%). In escitalopram group the common adverse events reported were headache (11%), nausea (11%), somnolence (8.3%) and the sexual adverse reported were decreased libido (8.3%). The rate discontinuation due to adverse events were not significant between two treatment groups.

DISCUSSION

The present study demonstrates the efficacy and safety of opipramol and escitalopram in the treatment of generalized anxiety disorders. The commonest symptoms presented in both groups were anxious mood, tension, insomnia and cardiovascular symptoms. At the baselines the mean total HAM-A scores were comparable between the groups. The opipramol proved to be equally effective in the treatment of GAD compared to escitalopram in terms of efficacy.

Opipramol is a sigma receptor agonist.[11] Because of its interesting receptor binding profile and with promising results in earlier trials, many studies were performed to explore the beneficial aspects of sigma receptor agonist. Opipramol has a high affinity for sigma-1 receptor with a weak affinity for H_1, sigma-2, $5HT_2$ and D_2 receptors and it lacks affinity for serotonin and noradrenaline reuptake sites. Sigma-1 receptor modulates calcium ion channels leading to the release of neurotransmitters, the dopamine and 5HT which in-turn results in the improvement of GAD symptoms. In one of the earlier studies the efficacy of opipramol was compared with placebo and alprazolam, the study showed there was a statistically significant reduction in total HAM-A score in opipramol ($p < 0.02$) and alprazolam ($p<0.004$) as compared to placebo.[12] In our study the opipramol showed a reduction of total HAM-A score after treatment, which was statistically significant and showed to be effective in treatment of GAD. The observations are similar to the above study.

In our study patients who were on opipramol for a duration of 4 weeks were well tolerated with minimal adverse effects. The commonly observed adverse effects in the study were head ache, dry mouth, tiredness and increased desire to sleep. The rate of adverse effects were less compared to escitalopram. All the adverse effects reported were mild to moderate in severity. The overall drop-out rate in the study was 22%, the main reason being non-compliance and loss of follow ups. Opipramol has been found to be well tolerated by the patients. Additional long term studies would be worthwhile to determine its safety on long term use.

Opipramol is widely prescribed in many European countries and Germany for the treatment of GAD.[11] This study was conducted to assess the efficacy of opipramol in Indian patients with standard available treatments. The study showed that opipramol is as effective as escitalopram in terms of efficacy, with a better tolerability profile than escitalopram.

CONCLUSION

This study demonstrates that Opipramol is effective and well tolerated in the treatment of GAD. It is noninferior in terms of efficacy compared to escitalopram. Further studies to evaluate long term safety and efficacy of opipramol relative to other established drugs for treatment of GAD appear warranted.

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