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Escitalopram Plus Flupenthixole Vs Paroxetine In The Treatment of Generalised Anxiety Disorder

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ABSTRACT

Aims The current study examines the efficacy of fixed dose combination of escitalopram plus flupenthixol in compared to paroxetine in treatments for generalized anxiety disorder (GAD). Method
Randomised, fixed-dose, parallel-group, 8-week study, with 60 patients: escitalopram plus Flupenthixole, (escitalopram 10 mg plus Flupenthixole .5 mg/day), (n=30); and paroxetine, 25 mg/day (n=30).
Results Mean change in the primary efficacy measure was greater with escitalopram plus Flupenthixole, at four weeks time, but almost equal at eigth week of treatment.
Conclusions Combining low dose Flupenthixole to Escitalopram may provide early response in generalised anxiety disorder at four to eight weeks of treatment in comparison to paroxetine.

KEYWORDS

INTRODUCTION

Pharmacological interventions that have good evidence for efficacy in treating GAD beyond benzodiazepines includes SSRIs, SNRIs, TCAs, pregabalin, quetiapine XR, and other therapies. Evidence from RCTs supports the use of SSRIs including escitalopram (Baldwin et al 2006; Bystritsky et al 2008) and sertraline (Ball et al 2005; Mokhber et al 2010], as well as the SNRIs duloxetine (Allgulander et al 2007) and venlafaxine XR (Allgulander et al 2008) for the first-line treatment of GAD. Similar evidence exists for paroxetine (Baldwin et al 2006; Kim et al 2006) supporting its use as a first-line option. Paroxetine CR has a similar active ingredient, and although there are less data supporting its use, it is likely interchangeable with paroxetine as a first-line agent (Gross et al 2006; Simon et al 2008). Some data suggest that escitalopram may be less effective than venlafaxine XR (Bose et al 2008) or quetiapine XR (Merideth et al 2012).

Flupenthixol is an antipsychotic neuroleptic drug. It is a thioxanthene, and therefore closely related to the phenothiazines. Recently it has generated renewed interest for the treatment of anxiety disorders. This study aimed to compare the efficacy of fixed doses of escitalopram plus Flupenthixole, (escitalopram 10 mg plus Flupenthixole .5 mg/day), with paroxetine (25 mg/day) as an active reference.

METHOD

Patients

The study was conducted at Indira Gandhi Institute of Medical Sciences (IGIMS), Sheikhpura, Patna, an autonomous organisation on the pattern of All India Institute of Medical Sciences, New Delhi. The institution provides super specialty medical facilities in Bihar. The study was approved by the institutional review board. The benefits and risks of study participation were fully explained to each patient, and written informed consent was obtained. This 8-week, randomized, double-blind, study was conducted from june 2015 to december 2015 at department of psychiatry. Patients either males or females who were aged from 18 to 60 years, diagnosed with generalised anxiety disorder at outpatient consultation, and consenting for the study. Those were assessed with demographic and clinical characteristic and base line HAM-A (Hamilton, 1959). Moreover, the intent-to-treat patients were required to have a score >14 in HAMA at the time of screening. Patients were excluded if they suffered from moderate to severe depression (HAM-D Score above 20). Patients were also excluded if they were at risk of suicide (according to the investigator's clinical judgement). The other exclusion criteria included unstable serious illness or serious sequelae of liver or renal insufficiency, or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic or metabolic disturbance were also excluded. Patients were excluded if they had taken psychoactive substances, anxiolytics, antidepressants and mood stabilizers within the 2 weeks before the screening visit, and any investigational drug or depot antipsychotics within 6 months before the screening visit and pregnancy or lactating mothers.

Study design

After baseline assessments, patients were randomly assigned to 08 weeks of parallel treatment with either fixed dose 25 mg Paroxitine, Extended release or combination of Escitalo-

pram 10 mg and flupenthixol .5 mg. on a once daily schedule at night. Patents were asked for regular follow up and were re assessed with HAM-A and side effects check list on 04 and 08 weeks of regular medications. Compliance with study treatment was monitored by pill counts, and affirmed from patients guardians. Patients with unsure compliance were dropped from the study.

Data Analysis

All efficacy analyses were conducted on the intention-to-treat population consisting of all randomised patients who took at least one valid post-baseline assessment of the HAM-A. The primary variables were change from baseline for total anxiety scores on the Hamilton anxiety scale. The data was analyzed using SPSS version 16.0. Normality of distribution of the data was assessed using Shapiro Wilk test which revealed that the data was normally distributed. Descriptive statistics was used for socio-demographic and clinical variables. Independent samples t test or chi-square test was used to compare the two groups across various socio-demographic and clinical variables t test was used to compare the HAM-A scores at baseline and subsequent 4th and 8th weeks of treatment.

Incidences of adverse events were compared between treatment groups and percentage calculated.

RESULTS:

The sample characteristic has been summarized in Table 1. The mean age of the patients of Escitalopram with flupenthxole combined group was 28.87 (SD 8.68) years, which was comparable to another group of patients treated with Paroxetine alone, 29.23 (SD 8.48) years. Year of education and total family income of both the group were comparable; p value .474 and .305 respectively. There was no significant difference among other socio demographic variables in between the two group; and the variables included gender, residence, family structure, occupation, marital status, religion and family history of psychiatric illness or medical and neurological illness. (Table-1)

"Table 1 about here".

Baseline HAM-A mean score of group A (Escitalopram + flupenthixole) patients was 43.15 (SD 3.20) and for group B (paroxetine alone) mean baseline score was 44.85 (SD 4.28). Using independent t test to compare these mean value found no significant difference. (Table 2)

When both group were reassessed on first follow up of four weeks with HAM-A, the mean score of group A was 31.11(SD 2.58) and for group B it was 34.91 (SD 2.36) (t =5.85, df=51.37, (P < .001). Reflecting better improvement of anxiety symptoms, with combination of escitalopram flupenthixole then paroxetine group. The assessment with HAM-A was repeated on second follow up after 8week for both group, the mean scores of group A and B was 27.38 (SD 3.44) and 29.64 (SD 2.79) respectively (t =2.81, df=58, (P > .001). Over all result indicates equally comparable improvement in both the group. (Table 2)

The mean change from baseline HAM-A score was also calculated at 4th and 8th week, for both the group. There was no difference among groups (t= -1.62, p= .110) for 4th week and (t= -.386, p= .701) for week 8 assessment. (Table 2)

"Table 2 about here". Figure 1 about here.

The side effect profile of Escitalopram plus flupenthxole and paroxetine is tabulated as actual incidence and percentage (Table 3). The most common side effects with Escitalopram plus flupenthxole was drowsiness, dry mouth, feelings of spinning and yawning Paroxetine caused dry mouth, drowsiness, constipation, insomnia and headache.

"Table 3 about here".

DISCUSSION:

The aim of the current study was to examine comparative efficacy of fixed doses of escitalopram (10mg) plus flupenthixol (0.5mg) v. Paroxetine (12.5 mg)for 08 weeks treatment of generalised anxiety disorder. The study also evaluated the comparative adverse effets of the treatment.

The primary efficacy analysis (mean change from baseline in HAM-A total score at week 4 and at week 8) showed that escitalopram 10 in combination with flupenthixol 0.5 were significantly superior to Paroxetine 25 mg. Antidepressants are now very well established treatment of GAD and antipsychotics in low doses are also an option for the treatment. This may be attributable to involvement of wider range of neurotransmitter in combination group. The reduced GABA ergic function is the most basic to any anxiety disorders, but the monoaminergic neurotransmitters (norepinephrine, serotonin, dopamine), glutamate and neuropeptide Y, substance P, are also involved in the pathophysiology of anxiety (Nemeroff, 2003). Hence antipsychotic use for early response in GAD may be justified nerubiologically.

However the change of HAM-A at week four was found to be more distinct, which were found to be losing advantage at eighth weeks. The trend of narrowing difference in response implicates no difference in long term but flupenthixole may provide an advantage of early response to usual SSRI efficacy in GAD. There has been various antipsychotics are being used successfully as an adjunctive to treatment resistant GAD (Lorenz et al,. 2010), but we also can use antipsychotics for early response.

The side effects reported by both the groups were almost same (table 3), dry mouth and drowsiness were the most common side effects in both groups.

The limitations of this study included the relatively small number of patients, the short duration of the treatment, and the single-centre nature of the study. The results of this 8-week trial could not generalize to longer periods of treatment, hence further large scale and longer study in rigorously designed would be warranted.

CONCLUSION:

In comparison to paroxetine, combining low dose Flupenthixole to Escitalopram may provide early response in generalised anxiety disorder at four weeks, which may equalises at eight weeks of treatment, without much difference in side effect

Table 1. Baseline demographic and clinical Characteristics of Patients treated with Escitalopram and flupenthixole combination or with Paroxitine 25mg.

		Escitalopram + flupenthxole (Mean ± SD) N = 26)	Paroxitine (Mean ± SD) N = 34)	t/x²	df	P value
Age (years)		28.87 ±8.68	29.23 ±8.48	-.166	57.96	.869
Years of Education		9.30 ± 4.18	8.50 ± 4.42	.720	58	.474
Total Family Income		27567 ±11714	24600 ±10457	1.035	58	.305
		N(%)	N(%)			
Sex	Male	14 (46.7)	13 (43.3)	.067	1	.795
	Female	16 (53.3)	17 (56.7)			
Residence	Urban	11 (36.7)	13 (43.3)	.298	2	.862
	Semi urban	13 (43.3)	12 (40.0)			
	Rural	6 (20.0)	5 (16.7)			
Family Structure	Nuclear	16 (53.3)	14 (46.7)	.267	1	.606
	Extended	14 (46.7)	16 (53.3)			
Occupation	Unemployed	9 (30.0)	10 (33.3)	.119	2	.942
	Self Employed	13 (43.3)	13 (43.3)			
	Service	8 (26.7)	7 (23.3)			
Marital Status	single	15 (50.0)	15 (50.0)	.000	1	1
	married	15 (50.0)	15 (50.0)			
Religion	hindu	13 (43.3)	10 (33.3)	.635	2	.728
	muslim	11 (36.7)	13 (43.3)			
	others	6 (20.0)	7 (23.3)			
Family History	None	22 (73.3)	23 (76.7)	.800	2	.670
	Psychiatric illness	4 (13.3)	5 (16.7)			
	Medical And Neurological Illness	4 (13.3)	2 (6.7)			

Table 2: Comparison of response of two treatment group on mean HAM-A scoring and change in ratings at 4 and 8 weeks compared to baseline.

	Escitalopram + flupenthxole (Mean ± SD) N = 26	Paroxitine (Mean ± SD) N = 34	t	df	P value
Baseline HAM-A	43.15 ± 3.20	44.85 ± 4.28	1.690	58	.096
HAM-A at 4th week	31.11 ± 2.58	34.91 ± 2.36	5.851	51.37	.000
HAM-A at 8th week	27.38 ± 3.44	29.64 ± 2.79	2.810	58	.007
Change of HAM-A Week 4	12.03 ± 4.88	9.94 ± 5.01	-1.623	58	.110
Change of HAM-A Week 8	15.76 ± 5.55	15.20 ± 5.63	-.386	58	.701

Table 3: Side effect frequency and percentage of both treatment groups.

	Side Effects	Paroxitine = n (%)	Escitalopram + flupenthixole = n (%)
1	Dry mouth	9 (26.5)	6 (23.1)
2	Drowsiness	9 (26.5)	8 (30.8)
3	Insomnia	5 (14.7)	3 (11.5)
4	Headache	5 (14.7)	2 (7.7)
5	Blurred Vision	0	0
6	Constipation	6 (17.6)	3 (11.5)
7	Diarrhea	1 (2.9)	1 (3.8)
8	Increased Appetite	3 (8.8)	1 (3.8)
9	Nausea / Vomiting	4 (11.8)	3 (11.5)
10	Sexual dysfunction	3 (8.8)	0
11	Light headedness	5 (14.7)	3 (11.5)
12	Spinning feeling	2 (5.9)	4 (15.4)
13	Tremor	5 (14.7)	2 (7.7)
14	Yawning	2 (5.9)	4 (15.4)

Figure 1: Mean Changes of HAM-A score over four and eight week assessments.

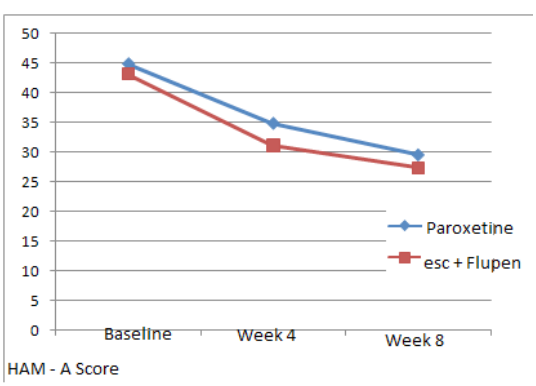

Figure 1: Mean Changes of HAM-A score over four and eight week assessments.

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