

## Escitalopram Versus Citalopram And Sertraline: A Double-Blind Controlled, Multi-centric Trial in Indian Patients with Unipolar Major Depression

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### ABSTRACT

The present randomized, double blind, parallel group, controlled, multi-centric trial was designed to evaluate the efficacy and tolerability of escitalopram in comparison with citalopram and sertraline in the treatment of major depressive disorder. Outpatients (N=214) with an ongoing/newly diagnosed ICD-10 major depressive episode and a Hamilton Rating Scale for Depression (HAM-D) score of > 18 were randomly assigned to citalopram, 20–40 mg/day (74 patients), escitalopram, 10–20 mg/day (69 patients) and sertraline, 50-150 mg/day (71 patients), for a 4-week double-blind treatment period, with dosage adjustment (after 2 weeks of treatment) according to the response to treatment. Clinical response was evaluated by the 17 items HAM-D and the Clinical Global Impression (CGI) scales, which were recorded at baseline and at weekly intervals. Tolerability was evaluated by observed/spontaneously reported adverse changes in laboratory parameters (baseline and after 4 weeks). Response rate was defined as a decrease in HAM-D score by 50% from baseline and remission rate was defined as a HAM-D score of < 8. Response rate at the end of two week were 58% for escitalopram (10mg/day), 49% for citalopram (20mg/day) and 52% for sertraline (50-100mg/day). Response rate at the end of four week were 90% for escitalopram (10-20mg/day), 86% for citalopram (20-40mg/day) and 97% for sertraline (100-150mg/day). The Remission rates at the end of four weeks were 74% for escitalopram, 65% for citalopram and 77% for sertraline. Adverse experiences were reported by 45% of patients in escitalopram group, 58% patients in citalopram and 56% patients in the sertraline group. Additionally, there were lesser dropouts and lesser requirement for dose escalation in escitalopram than in citalopram and sertraline group. In conclusion Escitalopram, the S-enantiomer of the citalopram is a safe and effective antidepressant in the Indian population. It has potentially superior efficacy than citalopram and a comparable efficacy to sertraline with fewer side effects than both citalopram and sertraline.

**Key Words :** Escitalopram, Sertraline, Citalopram, SSRI's.

### Introduction

Chirality, potentially offers one method to improve upon the SSRI (selective serotonin reuptake inhibitors) class. If all the serotonin reuptake inhibitory activity of racemic SSRI antidepressant resides in single isomer, it would be expected to be more potent than the racemate, and it might also be more selective (Hutt 2000; Tucker 2000). Thus, the clinical

development of that single isomer could improve both risks and benefits over the original antidepressant compound.

Escitalopram is the S-enantiomer of citalopram (SSRI); a racemic compound that has been demonstrated to be effective in the treatment of depression, panic disorder, premenstrual dysphoric disorder, and obsessive-compulsive disorder (Willett, 1999; Joubert, 1999; Keller, 2000).

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Substantial evidence indicates that escitalopram is responsible for the therapeutic efficacy of the racemate (Owens 2001). Escitalopram is over 100 times more potent as serotonin reuptake inhibitor than its stereoisomer, R-citalopram (Hyttel 1992; Sanchez 2000). In vivo studies of antidepressant action also support this conclusion; escitalopram is more potent and as efficacious as citalopram in various animal models of depression (Hyttel 1992; Mitchell 2001; Sanchez 2000; Montgomery 2001).

Escitalopram is therefore expected to offer several advantages over citalopram. Escitalopram theoretically should have at least twice the antidepressant potency of citalopram, since the therapeutic effects of citalopram are thought to be dependent upon serotonin reuptake inhibition and escitalopram appears to be responsible for virtually all of the serotonin reuptake inhibition produced by citalopram. Moreover, if any adverse effects of racemic citalopram were attributable to the R- enantiomer, they would be avoided in patients treated with the pure S- enantiomer.

The present multi-centric, parallel group study, examined the safety and efficacy of escitalopram in comparison with citalopram and sertraline (current standards of treatment) in Indian patients with major depressive disorder.

## Methods

A total of 11 centers in India participated in this controlled, randomized, double-blind, single dummy, titrable dose, parallel group, multi-centric study.

## Patients:

Eligible participants were male or female outpatients, 18 to 65 years of age, with ICD-10 diagnosis of Major Depressive Episode and a minimum score of 18 on the Hamilton Rating Scale for Depression (HAM-D).

Categories of patients included were:

- I. Newly diagnosed patients
- II. Previously diagnosed patients not responding to the prescribed antidepressants

Patients were excluded if they had 1) recent ongoing significant non-psychiatric medical disorder, 2) a history of substance abuse, 3) chronic suicidal ideation and behavior, 4) participated in any drug trial within 4 weeks, 5)

schizoaffective or bipolar disorder, 6) seizure disorder, 7) anorexia nervosa, 8) hepatic and renal system dysfunction, 9) therapy with lithium within the preceding month, 10) treatment with cimetidine, warfarin or MAO inhibitors, 11) hypersensitivity to citalopram, escitalopram and sertraline and non responders to citalopram and sertraline. Women of childbearing age not using contraceptives, pregnant women, lactating mothers, women desiring to have children, were also excluded.

## Study Design

The multi-centric trial was spread over diverse geographical locations in India. The study protocol was approved by the Institutional Review Boards for all participating study centers and by the Drug Regulatory Authority of India (Drug Controller General of India). The patients gave a signed informed consent before any study-related procedure (including screening) could be undertaken.

Patients underwent a comprehensive psychiatric and physical examination and appropriate investigations including hematology, biochemistry, ECG and urine pregnancy test (females). Patients meeting eligibility criteria at screening were enrolled in the study. Category I patients (Newly diagnosed) were started on drug therapy immediately. Category II patients (Non-responders) were started on trial drugs after a 1-week, single blind, placebo washout period (4 week for fluoxetine).

In order to maintain the blind, all double blind study medication was administered in alu- alu (aluminum – aluminum) strips. No other psychotropic drugs were allowed except a sedative/hypnotic (Benzodiazepine/ Nonbenzodiazepine) for treatment emergent anxiety/insomnia.

## Follow-up visits

Follow-up visits were after 1,2, 3 & 4 weeks of double blind treatment. Efficacy assessments included the 17-items HAM-D scale, CGI-I and CGI-S scale. Adverse events were enquired and recorded at every visit. Electrocardiogram (ECG), physical examination, and laboratory tests were performed at screening and at the end of week 4.

## Drugs and Dose Administration

The drugs were administered in the following manner as stated in the table below :

	Escitalopram				Citalopram				Sertraline			
	Morning		Evening		Morning		Evening		Morning		Evening	
Wk 1	Placebo		10mg		Placebo		20mg		Placebo		50mg	
Wk 2	Placebo		10mg		Placebo		20mg		Placebo		100mg	
If HAM-D score decrease 50% from the baseline after two weeks, the same dose was continued. Otherwise the dose was titrated upwards.												
	Responder		Non- Responder		Responder		Non- Responder		Responder		Non- Responder	
	Morn	Eve	Morn	Eve	Morn	Eve	Morn	Eve	Morn	Eve	Morn	Eve
Wk 3	P	10 mg	P	20mg	P	20mg	P	40mg	P	100mg	50 mg	100mg
Wk 4	P	10 mg	P	20mg	P	20mg	P	40mg	P	100mg	50 mg	100mg

Note: P= Placebo; Responder = HAM-D score reduced by 50% from the baseline; Morn = morning and Eve = Evening

### Primary Efficacy Measures

- 1) Change in HAM-D total score (The sum of all 17 items).
- 2) CGI –S score and CGI –I score.
- 3) Response rate: HAM-D score decrease by 50% from baseline.
- 4) Remission rate: HAM-D score below 8.

### Safety and Tolerability Measures

All adverse events volunteered, observed and enquired during the study or within 6 days of the last day of treatment were recorded. Additional information on the adverse event included date of onset, duration of event, concurrent therapies, the investigator's assessment of severity, possible cause relationship to study drug, and whether a change in dose or withdrawal of treatment was required. A 12 lead ECG was done at baseline and at the end of the study. Clinical laboratory tests, including routine hematology, serum chemistry and liver function tests were carried out at baseline and at end of study.

### Statistical Analysis

The three treatment groups were compared for the change in scores (from baseline) on various psychiatric scales. With the purpose of Intention To Treat (ITT), Last Observation Carried Forward (LOCF) approach was used.

Since the data for HAM-D were measured on ordinal scale, the data for these two parameters were subjected to Non-Parametric tests. The total HAM-D scores at each follow-up visit were subjected to Wilcoxon sign rank test for finding significant change from baseline (within group comparison). The data was subjected to Repeated Measures Analysis

Of Variance (RMANOVA) with baseline as covariate followed by Bonferroni post hoc test for week-by-week comparison between the treatment groups.

CGI-S and CGI-I scores were subjected to chi-square test for finding within-group significance.

Laboratory investigations data was first checked for its normality. If found normal, the data was subjected to parametric test (paired t test). Otherwise, the data was subjected to Non-Parametric (Wilcoxon Sing Rank) test for checking significance from baseline to last visit.

Treatment group comparisons of patient's demographic characteristics and baseline severity measurements were done using chi-square test and ANOVA. Fisher's exact test was used for categorical data where cell numbers were small. Statistical significance was defined as 2-sided p value < 0.05.

### Results

#### Demography

A total of 214 patients were randomized (balanced randomization) to receive either Escitalopram or Citalopram or Sertraline in the study. The demographic data for the patients are shown in Table 1. There was no statistically significant difference in the various demographic characteristics like age, gender, illness duration and illness severity among the treatment groups.

16 patients dropped out from the study. Of the 16 patients, 9 were in the Sertraline group, 3 in the Citalopram group and 4 in the Escitalopram group. The reasons for the dropout from the study are presented in Table 2.

Table 1.

**DEMOGRAPHIC PROFILE OF PATIENTS**

	Escitalo- pram (N=69)	Citalo- pram (N=74)	Sertra- line (N=71)
Males (n)	30	30	36
Females (n)	39	43	35
Age (years) (Mean+S.D.)	33+8	33+9	37+11
Duration of illness (Median months)	5.5	4	5
History of suicide attempt (n)	3	2	1
Severity of illness (HAM-D Score)(Mean+SD)	26 + 6	25 + 5	25 + 4
Severe (HAM-D=18-21) (n)	17	20	17
HAM-D Score (Mean+SD)	20 + 1	19 + 1	20 + 1
Very Severe (HAM-D>21) (n)	52	54	54
HAM-D Score (Mean+SD)	28+5	27+4	27+4

Table 2.

**DROP OUTS**

Reasons	Escitalopram	Citalopram	Sertraline
ADRs	1 <sup>a</sup>	2 <sup>b1-2</sup>	4 <sup>c1-4</sup>
Discontinua- tion on Pt's. request	1	0	1
Loss of efficacy	0	1	0
Reason not mentioned	2	0	3
Other Reasons	0	0	1
Total	4	3	9

a= Mild headache, nervousness & agitation which were considered of 'probable' causality. Headache required prescription medication. Study drug was discontinued.

b1= Throbbing headache which was considered of 'certain' causality. Headache required prescription medication. Study drug was discontinued.

b2= Study drug was discontinued after only 3 days of treatment because of G.I. side effects.

c1= Nausea & vomiting of moderate severity which were considered of 'certain' causality and required prescription medication. Study drug was discontinued.

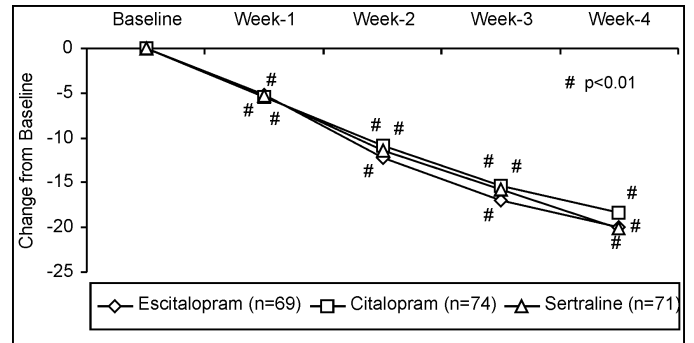
c2-3= Study drug was discontinued because of severe headache.

c4= Giddiness, vomiting & throbbing headache of moderate severity which were considered of 'certain' causality and required prescription medication. Study drug was discontinued.

**Efficacy**

The **HAM-D** score showed a significant decrease from baseline (within group) at each weekly assessment in the three treatment groups (Figure 1). However the difference between groups was not statistically significant at any assessment.

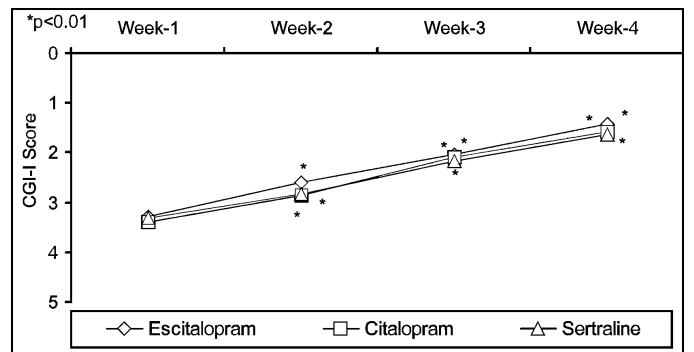
**Fig. 1. HAM-D scores, mean change from baseline**



No significant difference was observed between treatments, when the data was subjected to RMANOVA with baseline as covariate followed by Bonferroni post hoc test for week-by-week comparison.

The assessment of **global improvement (CGI-I)** showed that a statistically significant improvement (over baseline) occurred at the end of the study in each treatment group (Figure 2). However the difference between treatment groups was not statistically significant.

**Fig. 2: CGI-S Scores. Mean change from baseline**

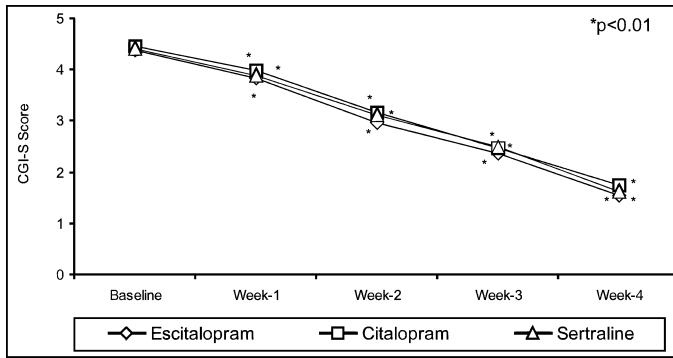


**The severity of illness (CGI-S)** decreased significantly with each of the treatment (Figure 3). The between treatment comparison did not show statistically significant difference at any assessment visit.

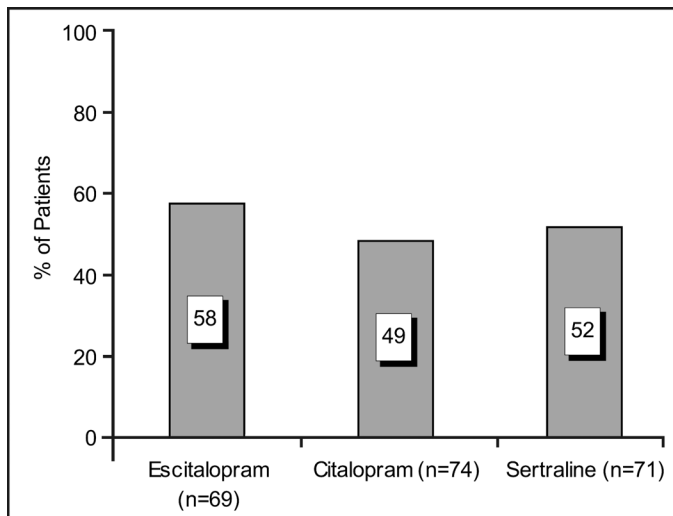
**Response rate at end of week 2 :** A 50% reduction (from baseline) in the total HAM-D score was observed in 58% patients in Escitalopram group (10mg) as compared to 49% in the Citalopram group (20 mg) and 52% in the Sertraline group (100mg) at the end of two weeks of treatment (Figure 4).

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**Fig. 3: CGI-S Scores. Mean change from baseline**

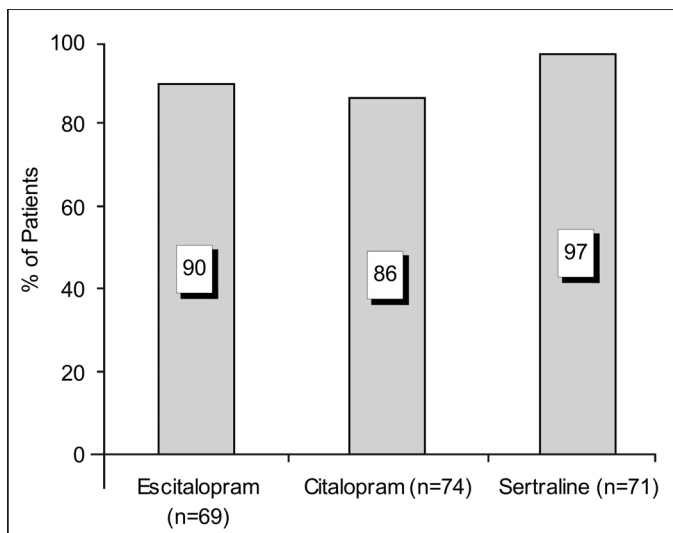


**Fig. 4: Responders at Week-2**



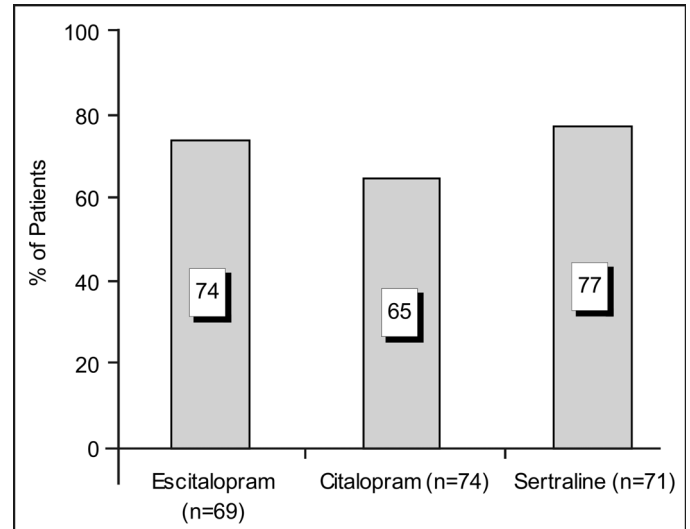
**Response rate at the end of week 4 :** Response rate after 4 weeks of treatment was 90% in Escitalopram group, 86% in Citalopram and 97% in Sertraline group patients (Figure 5).

**Fig. 5: Responders at Week-4**



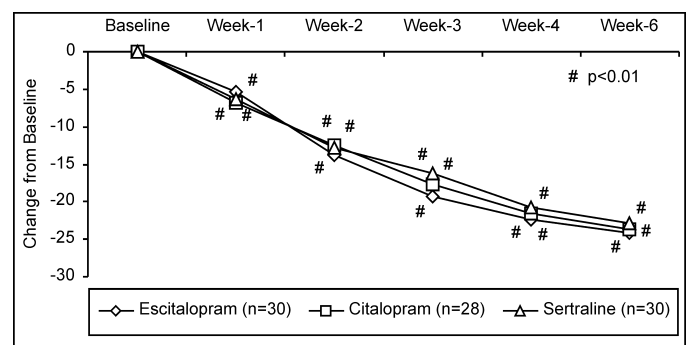
**Remission rate :** is defined as decrease in HAM-D total score to < 7. In Escitalopram group the remission rate was 74% as compared to 65% in Citalopram and 77% in Sertraline group patients after 4 weeks of treatment (Figure 6).

**Fig. 6: Remitted Cases at end of Week-4**



**Effect on Patients continued for 6 weeks :** Data from 88 patients who were continued for 6 weeks on study treatment showed that the trend (of change in HAM-D score in three groups) that was seen in the first four weeks was maintained over the next two weeks (Figure 7).

**Fig. 7: HAM-D scores, mean change from baseline (6 weeks)**

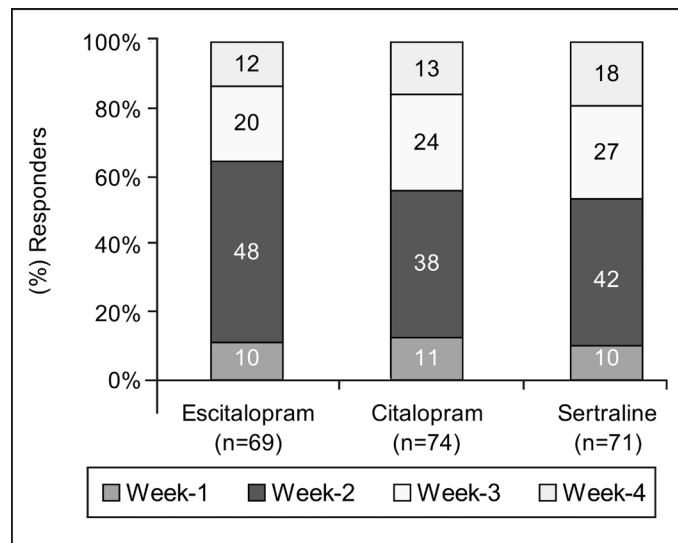


No significant difference was observed between treatments, when the data was subjected to RMANOVA with baseline as covariate followed by Bonferroni post hoc test for week-by-week comparison.

### Onset of action :

Proportionately more patients responded to Escitalopram (58%) and Sertraline (52%) as compared to Citalopram (49%) in the first two weeks of the therapy (Figure 8).

**Fig. 8: Onset of Action / Onset of Response**



**Safety:**

No serious adverse event was reported by any patient in the three treatment groups. The percentage of patients reporting adverse events was 45% in the Escitalopram group, 56% in the Sertraline group and 58% in the Citalopram group. No unexpected side effect was reported. The most common adverse events were headache [Sertraline (41%), Citalopram (24%), Escitalopram (17%)], gastrointestinal side effects [Sertraline (17%), Citalopram (15%), Escitalopram (9%)], giddiness [Sertraline (23%), Citalopram (14%), Escitalopram (10%)] and insomnia [Sertraline (13%), Citalopram (20%), Escitalopram (19%)] (Table 3).

Table 3.

**ADVERSE DRUG REACTIONS (ADR)**

	Escitalopram	Citalopram	Sertraline
N	69	74	71
Patients having ADR's n(%)	31(45)	43(58)	40(56)
Dropouts due to ADR's n	1	2	4
Headache n(%)	12(17)	18(24)	29(41)
G.I. Side Effects n(%)	6(9)	11(15)	12(17)
Giddiness n(%)	7(10)	10(14)	16(23)
Insomnia n(%)	13(19)	15(20)	9(13)
Anxiety n(%)	1(1)	3(4)	1(1)
Tremors n(%)	5(7)	7(9)	3(4)
Agitation n(%)	2(3)	5(7)	2(3)
Abnormal Ejaculation n(%)	2(3) <sup>§</sup>	3(4) <sup>§</sup>	1(1) <sup>§</sup>
Libido Decreased n(%)	0(0) <sup>§</sup>	1(1) <sup>§</sup>	2(3) <sup>§</sup>
Other ADR's # n	20(29)	23(31)	14(20)

◆ Note: patients may have had more than one ADR's  
 ◆ § = Incidence corrected for gender  
 ◆ # = Restlessness, Dry mouth, Somnolence, Yawning, Itching, Diaphoresis, Asthenia

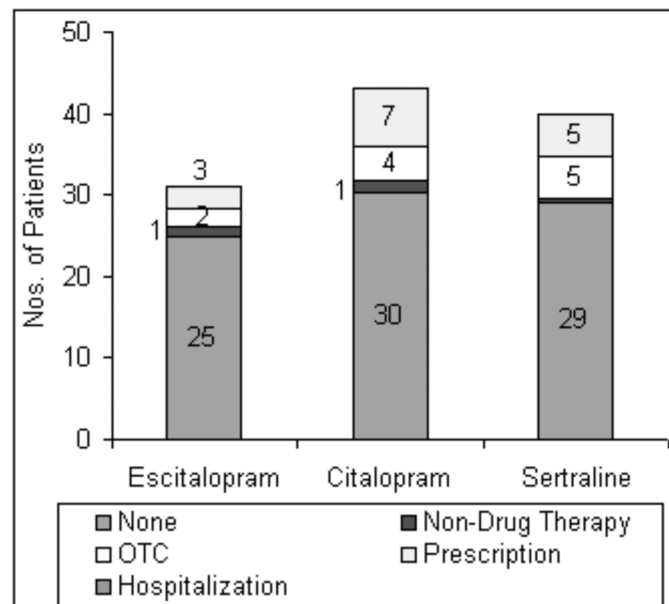
Most of the adverse events were mild in severity (Figure 9). Proportionately more people required OTC / prescription drugs in the Citalopram and Sertraline group as compared to Escitalopram (Figure 10). Most of these adverse events were causally not related to the drug treatment.

**Fig. 9: Severity of ADR's**



Note: Many subjects had more than one ADR

**Fig. 10: Management of ADR's**



Note: Some patients had more than one treatment

Sexual side effects (males) were reported by only a few patients in this trial. This is possibly because of the discomfort patients' feel in reporting such events.

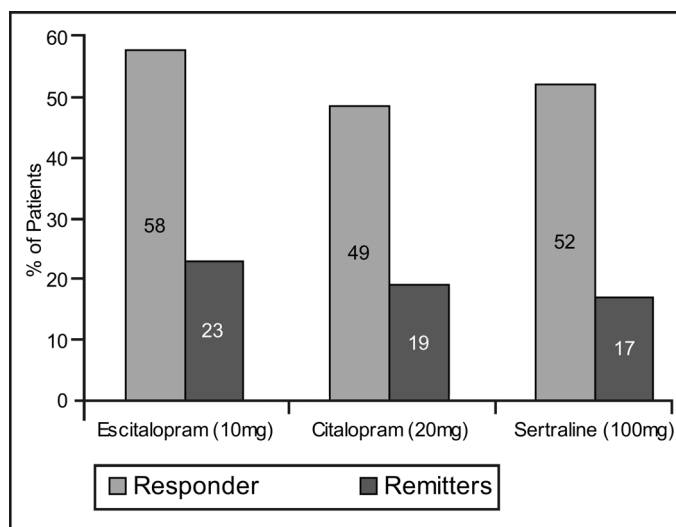
The laboratory investigations like hematology, biochemistry and ECG, carried out before and after treatment did not

show any clinically significant change from baseline in any treatment group.

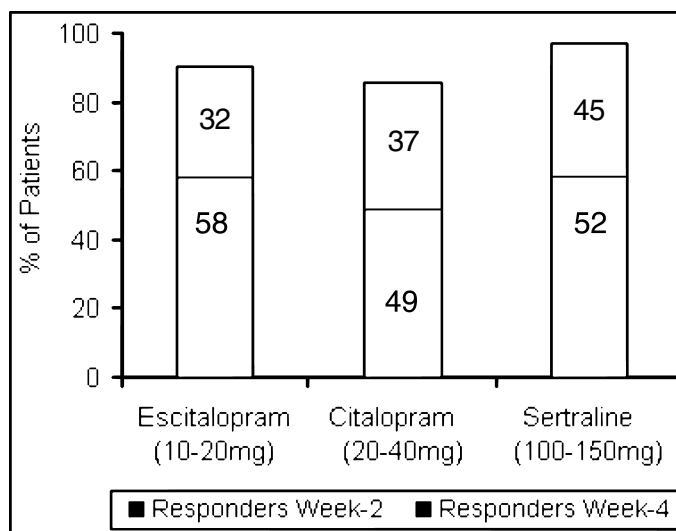
#### Dose response:

Proportionately more patients responded (58%) and remitted (23%) to initial dose (10mg) of Escitalopram as compared to Citalopram (49% & 19% respectively) and Sertraline (52% & 17% respectively) (Figure 11). On increasing the dose, the response and remission rate in Citalopram group were 86% & 65% respectively, as compared to Sertraline (97% & 77% respectively), and Escitalopram group (90% and 74% respectively), after four week of therapy (Figure 12 & 13).

**Fig. 11: Responders / Remitters To Initial Dosages**

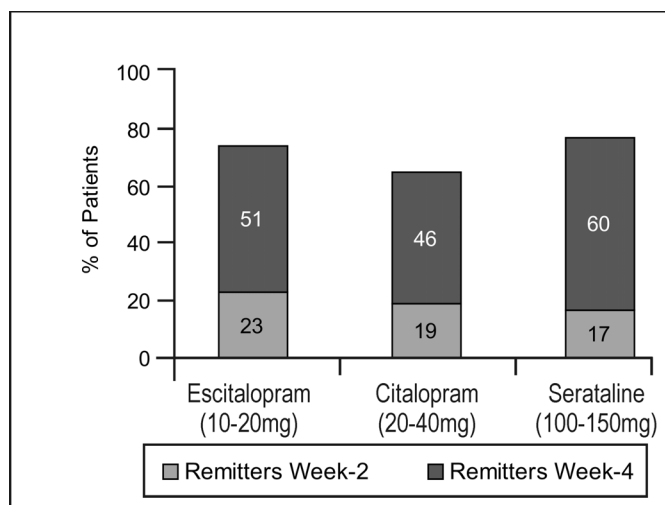


**Fig. 12: Total Responders After Dose Escalation**

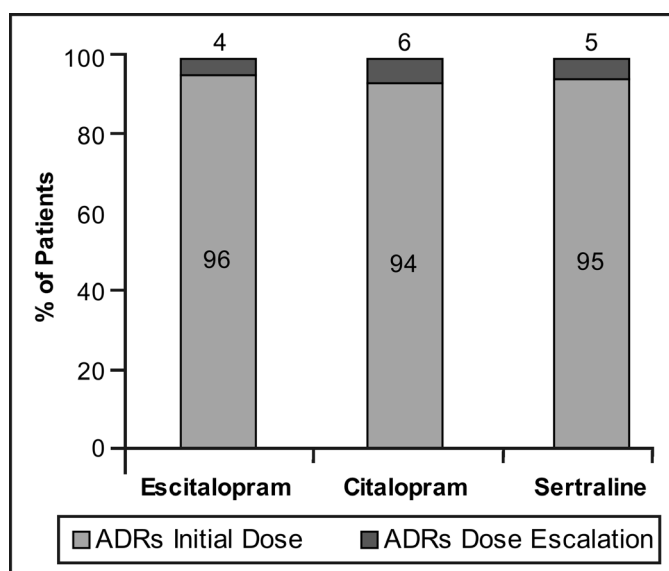


Most of the adverse events occurred during the initiation of the therapy i.e. with the initial dosages. Increasing the dose did not result in corresponding increase in the adverse events (Figure 14).

**Fig. 13: Total Remitters After Dose Escalation**



**Fig. 14: Dose Adverse Events Relationship**



#### Discussion

Enantiomers are non-superimposable, mirror-image type of isomers that have identical physio-chemical properties. They are distinguished on the basis of the differences in their ability to rotate polarised light.

Importantly, they can have different biological properties (pharmacodynamic and pharmacokinetic). This is because various receptors and other target proteins have chiral molecules in them and show stereo selectivity.

Recent advances in chiral technology and the ability to synthesize enantiomerically pure compounds, together with regulatory influences (FDA's Policy 1992, Brussels, CPMP 1993), have led the pharmaceutical industry to attempt, wherever relevant and possible, to develop new chemical

entities as single isomers. In parallel, there has been interest in “chiral switching”, the replacement of an already approved racemate by a single enantiomer. Potential advantages of chiral switching include an improved therapeutic index through increased potency and selectivity and decreased side effects; an improved onset and duration of effect; and a decreased propensity for drug-drug interactions.

Current therapy of depression requires improvement in many areas including 1) a requirement for a faster onset of action than provided by the current therapies [2-4 weeks]; 2) an increase in response rate; 3) a better long-term efficacy and safety; 4) efficacy in resistant depression; 5) efficacy in associated anxiety; 6) lesser number of dropouts.

Can chiral switching of the available antidepressants help in achieving these unmet needs in the therapy of depression? This question was explored in the present study where the S(-)-enantiomer of citalopram was compared against the standard anti-depressants sertraline and racemic citalopram.

The results of the study show that escitalopram produced greater mean changes in the HAM-D scores than citalopram through out the study period. There was also a proportionately higher response/ remission rate than citalopram. The differences however, could not reach statistical significance. This is mainly because of a small sample size. The trial was not designed (in terms of the subject numbers) to look for statistically significant differences between treatment groups. It was a trial done mainly to see the efficacy and safety of Escitalopram, the new antidepressant drug in Indian patients of major depression.

Data from 118 patients who were followed for additional two weeks (total of six weeks) was available. These patients were evenly distributed among the three treatment groups. The efficacy of the three drugs was minimally enhanced over the additional 2 weeks. As seen in the Figure 7, clear separation of escitalopram group profile from citalopram was maintained throughout the 6-weeks. Sertraline profile caught up with the escitalopram profile at week-4.

In the pivotal clinical trials conducted for the regulatory submission to USFDA, Escitalopram was seen to be more effective than placebo as assessed by standard study endpoints (change in MADRS, HAM-D & CGI scores) in randomized, double blind studies in patients with major depression. Efficacy analysis showed a significantly superior therapeutic effect for escitalopram versus placebo from

week 1 onwards (observed cases). By comparison, citalopram 20 mg/day did not demonstrate a statistically significant effect compared to placebo indicating faster onset of action of escitalopram. The difference between the active treatment groups was not statistically significant (William 2002).

In a meta-analysis by Azorin J.M. et al. (2004), data were pooled (506 patients) from three different clinical trials, each similar in design and inclusion/exclusion criteria, primary endpoints and assessment schedules. Among them, 169 received escitalopram, 171 received citalopram and 166 received the placebo. The primary efficacy parameter was the mean change from baseline to end of treatment in MADRS total score between escitalopram and citalopram groups. The change from baseline to endpoint of the Hamilton rating scale for Depression (HAM-D) and the Clinical Global Impression of Improvement and Severity (CGI-I and CGI-S) were also analysed as secondary criteria. Results showed that the mean change from baseline in the MADRS total score was significantly higher in the escitalopram group compared with the citalopram group (-17.3 vs -13.8 respectively,  $p=0.003$ ). This significant difference was observed as early as week 1 ( $p=0.01$ ). Response rates were significantly higher for escitalopram than for citalopram (56% vs 41% respectively,  $p=0.007$ ). A borderline significant difference was found for remission rate in the observed-cases analysis (43% vs 33% respectively,  $p=0.07$ ). Analyses of the HAM-D, CGI-I and CGI-S scores revealed consistent results. Sanchez C et al. (2004) reached to similar conclusions in their meta-analysis.

In vitro studies show that escitalopram has no or very low affinity for serotonergic or other receptors including alpha- and beta-adrenergic, dopamine, histamine, muscarinic, and benzodiazepine receptors. This suggests a very safe adverse effect profile. The common treatment emergent adverse events reported for escitalopram include insomnia, nausea, diarrhea and dizziness.

Similar side effect profile was seen in the present trial. In addition, headache was also reported commonly in this study. No adverse events were serious enough to require hospitalization. Majority of adverse events were mild to moderate in severity and required no treatment, resolving on their own over 2-5 days. In all treatment groups, the adverse events occurred mainly in the first two weeks of therapy. Adverse events occurred more frequently and with more severity in the citalopram and sertraline group. Consequently, there were greater dropouts in the sertraline group and more patients in sertraline and citalopram group



required 'Over The Counter' and 'prescription medicine' for the treatment of these adverse events.

There was one pointer to the claimed early onset of action of escitalopram in the present trial. This included a higher response rate to escitalopram in the first two weeks of therapy than citalopram/sertraline. It is possible that the response rate was less in sertraline group because the patients were on 100mg dose only for 1 week. However, the dosing regimen chosen for sertraline is the one, which is recommended in the package insert (ZOLOFT®).

Higher % of patients responded / remitted to 10 mg dose of escitalopram as compared to the initial dosage of citalopram (20 mg) & sertraline (50-100 mg). Dose escalation requirement was therefore less in escitalopram treated group.

### Conclusion

Chiral switching of racemic Citalopram to S (+) citalopram has resulted in a drug twice as potent as the racemic mixture. Additionally escitalopram has been shown to be more effective and better-tolerated drug than citalopram. It has also proved to be an equieffective and a safer alternative to Sertraline.

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