

ORIGINAL ARTICLE

**ESCITALOPRAM AND MIRTAZAPINE FOR THE
TREATMENT OF DEPRESSION IN HIV PATIENTS:
A RANDOMIZED CONTROLLED OPEN LABEL TRIAL**

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Abstract

Objective: The objective of this study was to compare the safety and efficacy of mirtazapine and escitalopram in HIV patients for the treatment of depression. **Methods:** In this trial, 70 adult HIV patients with major depression were randomized and assigned to receive 8 weeks of daily open label mirtazapine (5-30 mg) or escitalopram (7.5-20 mg). The primary outcome variables were endpoint response in Hamilton Rating Scale for Depression (HAM-D) score and change of HAM-D score from baseline to endpoint. Patients having improvement of $\geq 50\%$ on the HAM-D total scores during treatment were considered to have responded. A final 17-item HAM-D total score of 8 or less defined remission. **Results:** The response rate was 91.4 % (32/35) in Mirtazapine group and 85.7 % (30/35) in Escitalopram group ($p = 0.71$). The remission rate was more in escitalopram group (48.6 %, 17/35) compared to Mirtazapine group (34.3 %, 12/35); however it was not statistically significant (Chi square (1, N = 70) = 2.1, $p = 0.22$). After controlling for baseline score, the median HAMD score at 8 weeks was significantly lower in the Mirtazapine group (Median (Mdn)=4, Interquartile range (IQR)= 11) compared to Escitalopram group (Mdn=13, IQR= 12) ($p < 0.001$). The number of adverse events reported was more in Escitalopram group (110) than Mirtazapine group (85); however this was not statistically significant ($p = 0.34$). **Conclusions:** Both these drugs are useful in the management of depression in HIV patients and need further study. *ASEAN Journal of Psychiatry, Vol. 14 (1): January – June 2013: XX XX.*

Keywords: Escitalopram, Mirtazapine, Depression, HIV, Antidepressants

Introduction

Depression is the most prevalent psychiatric disorder among HIV-positive adults after the substance abuse. However, depression is also the most unattended condition in these patients [1]. The presence of depression in HIV patients affects their quality of life and adherence to

medication and diet regime [2]. There are many treatment options for the treatment of depression in HIV including conventional antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), novel agents such as dehydroepiandrosterone, psycho-stimulants and some psychotherapies, particularly interpersonal and group psychotherapy [3]. However, lack of

comparative studies made it difficult to draw a firm consensus regarding the best course of treatment [4]. Both escitalopram and mirtazapine have been used in the management of depression with good success reported across reviews and meta-analyses [5-6]. In this trial we compare the the safety and efficacy of mirtazapine and escitalopram in HIV patients for the treatment of depression.

Methods

This study was performed as a prospective, open, randomized, and parallel-group trial to compare the safety and efficacy of mirtazapine and escitalopram in HIV patients with depression. All the patients who satisfied the inclusion/ exclusion criteria and gave their voluntary written informed consent were randomized in 1: 1 ratio to receive either mirtazapine or escitalopram. After receiving the study medication at the baseline visit, patients were followed up for assessments at the end of Week 2, 3, 4, 6, and 8. Patients with HIV presenting to the OPD with symptoms of depression were evaluated. Patients of 18 years of age or older with HIV and on HAART for at least 6 months, who fulfilled the diagnostic criteria for depression as defined by DSM-IV, with HAM-D score more than 13 and MADRS score more than 19 were enrolled in the study. Pregnant or nursing women were not included in the study. The other exclusion criteria includes hypersensitivity to TCAs or SSRIs, previous use of mirtazapine or escitalopram, history of consumption of any psychotropic medication in the past 4 weeks, history of seizures, bipolar depression or other primary psychiatric diagnosis or abnormal lab results or serious disease that in the investigator's opinion should preclude their entry to the study.

Consenting patients who fulfilled the study selection criteria were randomized 1:1 to receive open-label treatment with either mirtazapine (starting dose, 15mg once a day, daily) or escitalopram (starting dose, 10mg once a day, daily). Randomization was done using a computer-generated list of random numbers. Both medications were prescribed to be taken

before going to bed. The patients were given respective medications in blister packs till the next follow up. The dose was up titrated i.e. mirtazapine to 30mg/day and escitalopram to 20mg/day if the improvement was less than 20% in the score of The Hamilton Rating Scale for Depression (HAM-D) [7] and Montgomery Asberg Depression Rating Scale (MADRS) [8] [both or any one of these] at the end of one month. The dose was down titrated i.e. mirtazapine to 5mg/day and escitalopram to 7.5mg/day if the patient complained of any adverse events any time during the follow up period, at the discretion of the investigator. Treatments with other psychotropic medications were not allowed to be prescribed to the subjects during study enrollment.

Demographics like age, sex and body weight were recorded at baseline before giving the trial medications. Patients were evaluated at baseline and every two weeks thereafter, until the study endpoint, using the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Rating Scale (MADRS), Clinical Global Impression Scales for Severity and Improvement (CGI-S and CGI-I) [9-10], Score on the insomnia subscale of HAM-D, Safety was determined through assessments of adverse events. All assessments were made by the same individual having experience in using the psychopathological scales.

At each follow-up visit, the patients were asked for any possible adverse events by non-leading questions. Any reported side effects were recorded in the adverse event form. The number and percentage of patients experiencing each specific event for Treatment-Emergent-Signs and Symptoms (TESS) (defined as experience that appeared for the first time during the study) were calculated for both treatment groups. The primary outcome variables were endpoint response in Hamilton Rating Scale for Depression (HAM-D) score and change of HAM-D score from baseline to endpoint. Patients having improvement of $\geq 50\%$ on the HAM-D total scores during treatment were considered to have responded. A final 17-item HAM-D total score of 8 or less defined

remission [11]. The secondary variables were (1) 50% or greater improvement in MADRS scores from baseline to endpoint; (2) Clinical Global Impression (CGI) severity scores of 1 or 2 at endpoint; (3) CGI improvement scores at endpoint; (4) Score on insomnia subscale of Hamilton scale; and (5) Score on insomnia subscale of Montgomery scale at endpoint; (6) Percentage of adverse events reported in each group.

The study was conducted in accordance with the Helsinki Declaration after the approval of Hospital Ethics Committee. Before enrollment in the study, the objectives, methods of the study and other necessary issues related to the protection of human rights were explained to the patients. Written informed consent was obtained from all patients on a voluntary basis prior to the enrollment in the study.

Statistical analysis

The analysis was performed on data from the intention-to-treat sample. Baseline characteristics for efficacy and safety outcomes were summarized using means/ standard deviations for interval/ratio variables, frequency/percentage for nominal variables and median/ interquartile range for ordinal variables. The last observation was carried forward to an estimate missing data for patients who withdrew the prior of completing 8 weeks of treatment. The remission rate between two groups was analysed for significance by chi-square test while the response rate was analysed by Fisher's exact test. In view of the incomparable baseline scores, the endpoints (HAM-D score and

MADRS score) were analysed using an analysis of covariance model (ANCOVA) after the rank transformation to correct for baseline differences [12]. The model included terms for treatment as a fixed effect and the baseline measurement as a covariate. The aim was to assess the treatment differences. The MADRS scores and Clinical Global Impression (CGI) severity scores at endpoint were dichotomized and analyzed for the significance with Chi square test or Fisher's exact test when any of the expected value was less than 5. The CGI improvement scores, score on insomnia subscale of Hamilton scale and Montgomery scale at endpoint were compared between groups using Mann-Whitney's U test. The change in score on insomnia subscale of Hamilton scale and Montgomery scale at endpoint was analyzed for significance using Wilcoxon Signed-rank test. The safety analyses were conducted on data from patients who received at least one dose of a study drug. The rate of adverse events was compared between treatment groups with Chi square test or Fisher's exact test when any of the expected value was less than 5. All the Statistical tests performed were two tailed and p-value < 0.05 was considered to be statistically significant. The data was analyzed using the Statistical Package for Social Sciences (SPSS) version 17.

Results

Participants' characteristics at entry

The randomisation of treatment (participant flow in the trial) is shown in the figure 1. The demographic and clinical characteristics of participants at baseline are shown in Table 1.

Figure 2: Participant flow through the trial.

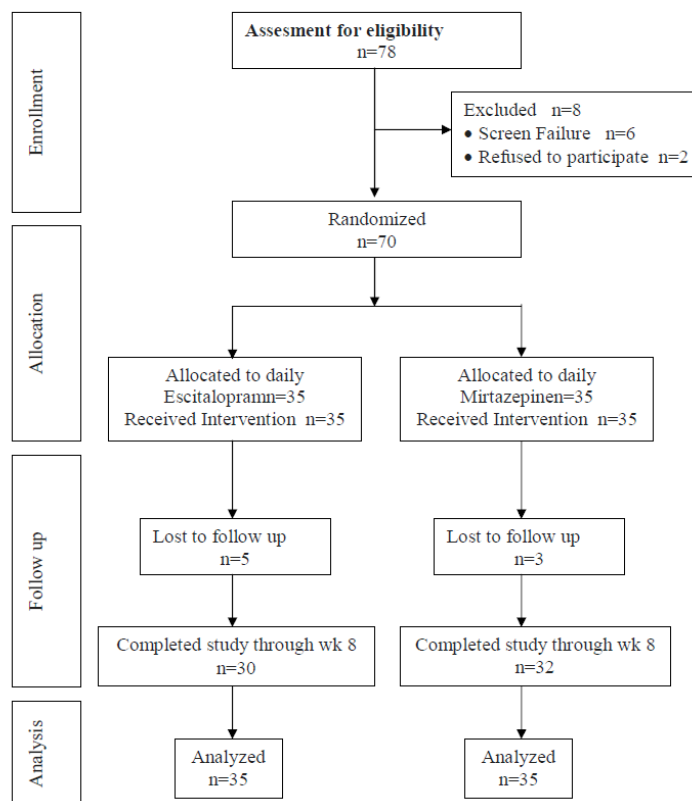


Table 1. Baseline demographic and clinical characteristics of the study participants.

Demographic characteristics	Group 1 (Escitalopram) n=35	Group 2 (Mirtazepine) n=35	Total	p- value
Sex ¹				
Male	14 (60.0)	16 (45.7)	30 (42.9)	p = 0.63 ^a
Female	21 (40.0)	19 (54.3)	40 (57.1)	
Age (Years) ²	37.86 ± 7.7	36.8 ± 8.2	37.34 ± 7.9	p = 0.41 ^c
18-30	4	6	10	
31-40	21	22	43	
41-50	7	4	22	
>50	3	3	6	

Weight (Kg)²	52.5 ± 9.3	50.4 ± 8.2	51.4 ± 8.8	p = 0.31 ^b
HAM-D score³	36 ± 6	38 ± 7	36.0 ± 7	p = 0.01 ^c
MADRS score³	42 ± 12	45 ± 8	44 ± 9	p = 0.06 ^c
CGI Severity score³	5 ± 2	6 ± 1	5 ± 1	p = 0.04 ^c
Insomnia Hamilton scale³	5 ± 3	6 ± 1	6 ± 1	p = 0.05 ^c
Insomnia Montgomery³	5 ± 1	5 ± 0	5 ± 1	p = 0.12 ^c

^a= Chi square test, ^b= Student's t test, ^c= Mann Whitney U Test

¹ = Data expressed as frequency (Percentage)

² = Data expressed as mean ± one standard deviation

³ = Data expressed as median ± one interquartile range

Table 2. Comparison of response and remission rates between the treatment groups.

	Group 1 (Escitalopram) n=35	Group 2 (Mirtazepine) n=35	p-value
Response Rate (≥50% decrease in baseline HAM-D Score at week 8)	30 (85.7)	32 (91.4)	p = 0.71 ^a
Remission rate (8 week HAM-D Score ≤ 8)	17 (48.6)	12 (34.3)	p = 0.15 ^b

*Data expressed as frequency (percentage)

^a= Fisher's exact test, ^b= Chi square test

The two treatment groups were balanced at entry with regard to the demographic variables. The severity of depression was higher in Mirtazapine group patients (Mdn HAM-D score 38, IQR= 7; Mdn MADRS score 45, IQR= 8; and Mdn CGI severity score 6, IQR= 1) compared to Escitalopram group (Mdn HAM-D score 36, IQR= 6; Mdn MADRS score 42, IQR= 12; and Mdn CGI severity score 5, IQR= 2) as indicated by higher baseline scores in Hamilton (p=0.01), Montgomery (p=0.06) and CGI severity (p=0.04) scales.

Efficacy

The response rate (i.e. >50% decrease in baseline HAM-D Score at week 8) was 91.4 % (32/35) in Mirtazapine group and 85.7 % (30/35) in Escitalopram group (p= 0.71). The remission rate (i.e. HAM-D score of less than or equal to 8 at 8 weeks) was more in escitalopram group (48.6 %, 17/35) compared to Mirtazapine group (34.3 %, 12/35); however it was not statistically significant (Chi square (1, N = 70) = 2.1, p = 0.22) (Table 2). After controlling for baseline score, the median HAMD score at 8 weeks was

significantly lower in the Mirtazapine group (Mdn=4, IQR= 11) compared to Escitalopram group (Mdn=13, IQR= 12) ($p < .001$). The median MADRS score at 8 weeks, after controlling for baseline score, it was also significantly lower in the Mirtazapine group (Mdn=7, IQR= 12) compared to Escitalopram group (Mdn=17, IQR= 15) ($p < .001$). The number of patients with greater than or equal to 50 % decreases in baseline MADRS Score at 8 weeks did not differ significantly in Mirtazapine

(30/35) or Escitalopram group (32/35) ($p = 0.71$). The number of patients with Clinical Global Impression (CGI) severity scores of 1 or 2 at 8 weeks were more in the Mirtazapine group (23/35) than Escitalopram group (18/35); however this difference was not statistically significant ($p = 0.22$). The Median CGI improvement score at 8 weeks was significantly lower in the Mirtazapine group (Mdn=1, IQR=1) than Escitalopram group (Mdn=2, IQR=2) ($p < 0.001$) (Table 3).

Table 3. Comparison of other outcome variables between treatment groups at end point (8 weeks).

	Group 1 (Escitalopram) n=35	Group 2 (Mirtazepine) n=35	p- value
HAMD score (after controlling for baseline) at 8 weeks	13 $\pm$ 12	4 $\pm$ 11	$p < 0.001^a$
MADRS score (after controlling for baseline) at 8 weeks	17 $\pm$ 15	7 $\pm$ 12	$p < 0.001^a$
Patients with ≥ 50 % decrease in baseline MADRS score at 8 weeks	32 (91.4)**	30 (85.7)**	$p = 0.71^b$
Patients with CGI severity scores of 1 or 2 at 8 weeks	18/35 (51.4)**	23/35 (65.7)**	$p = 0.22^c$
CGI improvement score at 8 weeks	2 $\pm$ 2	1 $\pm$ 1	$p < 0.001^d$
Score on insomnia subscale of Hamilton scale at 8 weeks	3.0 $\pm$ 4	0.00 $\pm$ 0	$p < 0.001^d$
Score on insomnia subscale of Montgomery scale at 8 weeks	4.0 $\pm$ 2	0.00 $\pm$ 0.00	$p < 0.001^d$

*Data presented as median $\pm$ one interquartile range unless otherwise specified

**= Data presented as frequency (percentage)

^a= Rank analysis of covariance, Covariate = baseline score

^b= Fisher's exact test, ^c= Chi square test, ^d=Mann Whitney U test

Compared to baseline, there was a significant decrease in Score on insomnia subscale of Hamilton scale at 8 weeks in escitalopram group (Mdn=5.0, IQR=3 to Mdn=3.0, IQR=4) ($Z = -2.965$, $p = 0.003$, $r = 0.35$) as well as in mirtazapine group (Mdn=6.0, IQR=1 to Mdn=0.00, IQR=0) ($Z = -5.206$, $p < 0.001$, $r = 0.62$). The Score on insomnia subscale of Montgomery scale was also significantly lower at 8 weeks (Mdn=4.0, IQR=2) compared to baseline (Mdn=5.0, IQR=1) in escitalopram group ($Z = -3.730$, $p < 0.001$, $r = 0.44$) as well as

in mirtazapine group (Mdn=5.0, IQR=0 to Mdn=0.00, IQR=0, $Z = -5.144$, $p < 0.001$, $r = 0.61$) (Table 4). Compared to escitalopram group (Mdn=3.0, IQR=4), the Score on insomnia subscale of Hamilton scale at 8 weeks was significantly lower in the mirtazapine group (Mdn = 0.00, IQR=0, $U = 176.5$, $Z = -5.661$, $P < 0.001$, $r = 0.68$). The Score on insomnia subscale of Montgomery scale at 8 weeks was significantly lower in the mirtazapine group (Mdn= 0.00, IQR=0.00) compared to escitalopram group (Mdn=4.0, IQR=2, $U = 172.5$, $Z = -5.665$, $P < 0.001$, $r = 0.68$).

Table 4. Comparison of change in scores of insomnia subscale of Hamilton and Montgomery depression scale between treatment groups.

Decrease in Scores on Insomnia	Group	Baseline	Score at 8 weeks	p- value ^a
Decrease in Score on insomnia subscale of Hamilton scale at 8 weeks compared to baseline	Group 1 (Escitalopram) n=35	5.0 $\pm$ 3	3.0 $\pm$ 4	p < 0.01
	Group 2 (Mirtazapine) n=35	6.0 $\pm$ 1	0.00 $\pm$ 0	p < 0.001
Decrease in Score on insomnia subscale of Montgomery scale at 8 weeks compared to baseline	Group 1 (Escitalopram) n=35	5.0 $\pm$ 1	4.0 $\pm$ 2	p < 0.001
	Group 2 (Mirtazapine) n=35	5.0 $\pm$ 0	0.00 $\pm$ 0	p < 0.001

*Data presented as median $\pm$ one interquartile range

^a=Wilcoxon Signed-rank test

Table 5. Adverse Events According to Treatment Group.

Adverse Events	Group 1 (Escitalopram) n=35	Group 2 (Mirtazapine) n=35	p- value
Total number of adverse events	110	85	p = 0.34 ^a
Anxiety	16 (45.7)	9 (25.7)	p = 0.08 ^b
Nausea/vomitting	20 (57.1)	16 (45.7)	p = 0.17 ^b
Memory/concentration problems	14 (40)	8 (22.9)	p = 0.06 ^b
Dry mouth	18 (51.4)	12 (34.3)	p = 0.07 ^b
Loss of libido	7 (37.1)	3 (28.6)	p = 0.17 ^b

Premature ejaculation	3 (17.1)	2 (5.7)	$p > 0.99^c$
Suicidal thoughts	5 (31.4)	3 (25.7)	$p = 0.71^c$
Constipation	10 (28.6)	12 (34.3)	$p = 0.60^b$
Dizziness	11 (31.4)	7 (22.9)	$p = 0.27^b$
Sedation	4 (11.4)	8 (25)	$p = 0.20^b$
Abnormal dreams	2 (22.9)	5 (37.1)	$p = 0.43^c$

*= Data presented as frequency (percentage)

^a= Student's t test, ^b= Fisher's exact test, ^c= Chi square test

Safety and tolerability

The number of adverse events reported were more in Escitalopram group (n = 110) than Mirtazapine group (n = 85); however this was not statistically significant ($p = 0.34$). The number of adverse drug events reported by the patients is shown in Table 5. The common adverse events include anxiety, nausea, vomiting, memory problems, dry mouth, constipation, and dizziness. The most common adverse event was nausea and vomiting in Mirtazapine (16/35) as well as escitalopram group (20/35). The adverse events did not differ significantly between the two groups. Most of the adverse events in both the treatment groups were mild to moderate and did not lead to discontinuation of treatment. No serious adverse reaction was reported by any patient from either group.

Discussion

Mental disorders are common in HIV-infected persons globally. The most common psychiatric diagnoses among HIV-positive individuals are mood and anxiety disorders, particularly MDD and other depressive disorders. The efficacy and tolerability of both the drugs escitalopram and mirtazapine in the study was in keeping with studies using the two drugs in depressed subjects [13-14]. No specific side effects related to the immune-compromised state of the patients was noted. There is no specific drug of choice with regard to the management of depression in HIV patients [15]. The following study demonstrates the usefulness of both of these drugs in this

population while highlighting the need for further studies in this arena.

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