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Double blind, randomised trial to compare efficacy of escitalopram versus citalopram for interferon induced depression in hepatitis C patients

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A B S T R A C T

Objectives: The objective of the study was to compare the two antidepressant drugs citalopram and escitalopram on the basis of efficacy in depressed patients of Hepatitis C patients receiving interferons.

Methods: In this double blind randomized trial, the hepatitis C patients visited National institute of liver and Gastro intestinal diseases (NILGID), Dow University Hospital, were screened for depression before starting treatment with interferons. The Institutional review board approval was obtained and its letter reference no.is: IRB-682/DUHS/Approval/2016/169. Patients with previous history of depression were excluded from the study. The patients who started with Interferon therapy were assessed for depression on baseline and then on each visit. Those who developed depression were randomly assigned to receive either citalopram or escitalopram. Treatment groups were assessed with depression scale each time they visit the clinic. Two antidepressants were compared for their efficacy at an interval of 4 weeks, 8weeks and then 12 weeks.

Results: In the current study 80 patients were randomized to receive either citalopram or escitalopram. The study outcome was better in patients treated with escitalopram. The mean change in depression score from baseline to the end of the study was greater in escitalopram group i.e. 10.41 as compared to citalopram group i.e. 14.17. The difference in depression score was also calculated as 4.28 and.
3.76 ($p < 0.001$) for both the drugs at week 8 and week 12 respectively, which was statistically significant. Difference in depression score were also calculated for gender 0.576 ($p = 0.497$) and age 0.950 ($p = 0.265$), which were found to be non-significant, statistically.

Conclusion: The results demonstrated superiority of escitalopram over citalopram, the drug is twice as potent as the racemic mixture. Additionally the drug is well tolerated and exhibited better effects. Escitalopram proved to be a safer alternative to citalopram.

1. Introduction

Hepatitis C virus (HCV) is a leading public health problem. It is estimated that 130–150 million people are affected by this lethal disease worldwide [1]. Chronic HCV infection is currently the major cause of hepatic carcinoma and liver cirrhosis and has become the main reason for liver transplantation [2,3]. (see)

There is no vaccine and prophylactic treatment available for the prevention and control of HCV infection, preventive measures should be practice in health care system [4].

Treatment strategy for chronic hepatitis C infection typically involves the use of interferons with oral antivirals like Ribavirin [5].

Interferon (IFN) is a potent cytokine with antiviral, immunomodulating and antiproliferative properties produced by the human blood [6]. These are the proteins that are synthesized and release by body cells in response to any inducer (like viruses), to develop an antiviral state. They act as defense proteins by activating the immune cells like macrophages and natural killer cells [7].

Although treatment with interferon alpha is effective in HCV infection, it is also associated with some serious adverse effects on central nervous system. The symptoms include anorexia, fatigue, and loss of concentration, lethargy, sadness, anger, social isolation and sleep disturbances [8].

Continuous use of interferons may develop major depression that decreases the quality of patient's life and results in suicidal thoughts, therefore regular monitoring is needed during therapy [9,10].

Depression caused by interferons may be associated with activation of inflammatory response system (IRS) [11,12]. The main findings are increased proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α [13].

IRS activation interferes with serotonergic metabolism that is followed by major depression. Patients treated with interferons have reduced presynaptic 5-HT neuron activity that results in decreased serum level of tryptophan (serotonin precursor) [14]. Tryptophan plays

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a substantial role in developing mood disorders [15].

IFN use may also reduce the concentration of serotonergic receptors in central nervous system [16,17].

To treat the depression that is associated with disturbance in serotonin pathway SSRIs are the most convenient and suitable antidepressants available [18]. The two widely prescribed SSRIs are citalopram and escitalopram. The recommended dose for escitalopram is 10 mg/day half of the dose of citalopram i.e. 20 mg/day [19–21].

The SSRI citalopram used conventionally in treating major depression is a racemic mixture that is composed of 2 enantiomers, S (+) enantiomer that is called escitalopram and an R (−) enantiomer that is called R-citalopram in the ratio 1:1 [Fig. 1] [22].

2. Method

The study was conducted at National Institute of liver and GI diseases (NILGID), Dow University Hospital. This study was approved by institutional review board (IRB) of Dow University of Health Sciences (DUHS), Karachi, reference no.is IRB-682/DUHS/Approval/2016/169 and was carried out in accordance with the Guideline for Good Clinical Practice and the Declaration of Helsinki. Care and medication for depression were free of charge for the patients enrolled in the trial. Before entering the trial all patients filled the informed consent form.

Subjects were enrolled by interviewing using the depression scale i.e., Aga Khan University Anxiety and Depression Scale (AKUADS). Before the start of anti-viral treatment at screening visit, Depression was assessed utilizing depression scale (AKUADS) and patient were labeled depressive when score of 19 was documented. Patients scored 19 or more than 19 at baseline were excluded from the trial. Interferon & Ribavirin therapy was initiated in patients with no signs of depression. The dose of interferon was 3 million international units subcutaneously thrice a week and the dose of Ribavirin was 400 mg twice a day. Patients were scheduled to visit initially at two weeks after start of Ribavirin and Interferon and then at every 4 weeks. At any point, while depression was diagnosed, patients were enrolled to be randomized to receive either of the two treatment groups. A statistician made the randomization list with 40 patients treated with escitalopram and 40 patients treated with citalopram. Treatment groups were monitored for depression at every visit up to end of the therapy.

Citalopram and Escitalopram were dispensed in lookalike capsule shells. Study investigators and participants were blind to the study medications and code number was assigned to the capsules packet.. The study medication was stored at Inpatient Pharmacy department of Dow University Hospital and codes were kept in sealed envelopes. The initial dose for escitalopram was 10 mg and 20 mg for citalopram orally once daily [Table 1].

The eligible age of patients for trial was 18–60 years. Gender included both male and female patients. No healthy volunteers participated in the study.

Patients with chronic hepatitis C, detected by HCV-RNA test, with an indication for anti-viral treatment with interferon and ribavirin, and who had provided written informed consent were considered eligible for the study.

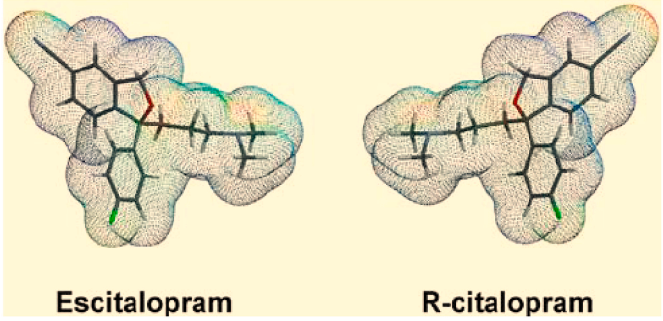
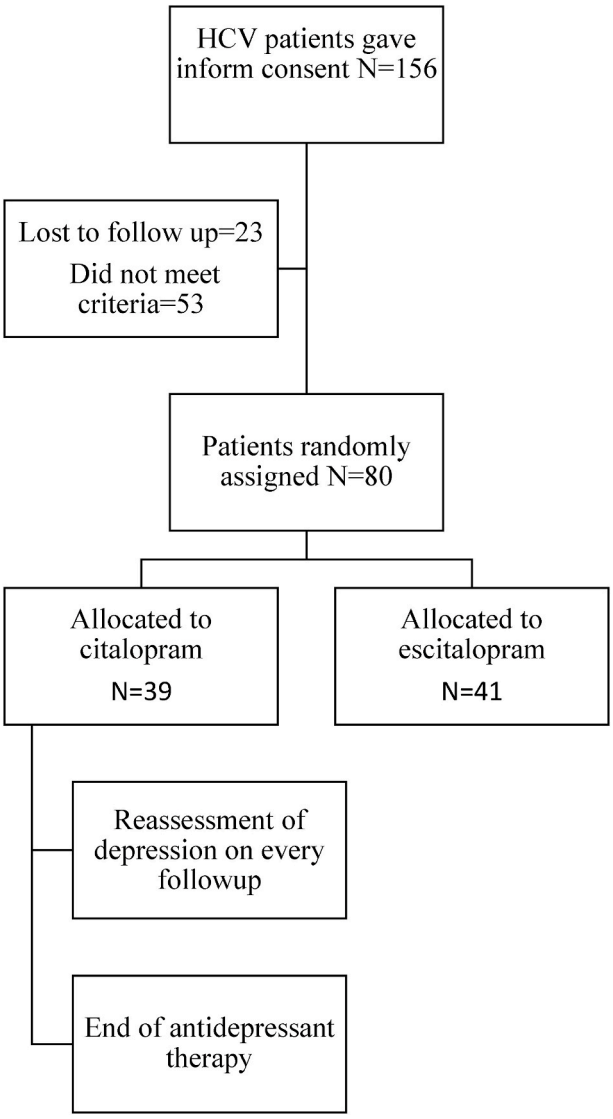


Fig. 1. Two enantiomers of citalopram. Enantiomers are mirror images of each other.

Table 1
Schematic representation of research design..



Individuals were excluded from participating in the study in case of advanced liver disease, serious internal diseases (cancer, autoimmune diseases, and heart diseases), or with any co-infections (Hepatitis B virus or HIV).

Patients who already were on antidepressant therapy or diagnosed depression at baseline or have any other psychiatric disorder were excluded from trial.

Additionally patients with the history of severe drug allergies or hypersensitivity, serious illness, presence of contra-indications for HCV therapy, abnormal thyroid hormone values or drug abusers, were excluded from the trial.

Pregnant or breastfeeding women were also excluded from the study.

The trial was conducted during December 2014 to August 2016, within period of 21 months.

Patients with positive HCV-RNA at NILGID clinics, who were eligible for treatment with interferon and ribavirin.

Depression was assessed using AKUADS (Aga khan university anxiety depression scale). It is a 25-item questionnaire with dimensions anxiety

and depression. This questionnaire was chosen because its entire items refer to GI and emotional state and also covers somatic symptoms. This questionnaire is available in Urdu language and easily understood by local population. According to questionnaire's manual, the cutoff value was set 19 or greater.

During initial visit patient's history, medication history and disease history was taken on pre designed screening visit form. The form included information about disease status, planned treatment, co-morbid, and depression score.

General physical examination of patients was also done that includes monitoring of blood pressure, heart rate, temperature, height and weight.

During each follow up visit examination of patients was done and their doses were adjusted according to recommendation of psychiatrist. Follow up information was taken on follow up form that included questions regarding symptoms, disease status, depression score and presence or absence of any side effects.

2.1. Statistical analysis

The sample size was calculated by using PASS version 11. Repeated measure ANOVA with 95% confidence interval and 80% power of the test, with mean of Escitalopram and citalopram 36.91 and 37.55, 15.36 and 16, in baseline and up to 4 weeks.

Calculated Sample size was 30 patients per group. 40 patients were included in each group including 10 patients as drop out. So the total sample size was calculated as 80.

Trial data was analyzed by statistical software IBM SPSS Statistics data editor version 21.0. Finally results were calculated on frequency basis and percentages. All results are shown in graphs with percentage basis, frequency and percentages are calculated for all categorical variables, bar graphs and pie were constructed for variables to show findings and mean and standard deviation were calculated for quantitative variables.

Furthermore independent samples *t*-test and Man-Whitney u test were applied to calculate mean depression score between two subgroups on the basis of drug, gender and age. Independent sample *t*-test was used to calculate depression score at week 12th and week 8th because data followed normal distribution. Man-Whitney *U* test was used for calculating depression at week 4 and baseline because data did not follow normal distribution. The main efficacy parameter was difference in mean change of depression score at week 12 between escitalopram and citalopram groups. Statistical significance was accepted at the 95% confidence level ($P < 0.05$).

3. Results

A randomized, double blind study was conducted and a total of 156 patients were screened at the outpatient department (OPD) of NILGID, Dow University Hospital and gave written consent to participate in the study. Out of 156 patients 23 patients were lost to follow up, 80 patients met the criteria for the study and were randomized and 53 patients did not met the criteria. So, total 80 patients were enrolled in the study. All patients information was collected on pre designed proforma at screening visit. Major parts of proforma included patients age, gender, enrolment date, QHCV RNA quantity, depression score and any co-morbid present.

Relevant demographic data and baseline depression score of patients with chronic Hepatitis C enrolled in study are summarized in Table 2. The mean age of the patients was 43 years. The ratio of female patients was higher than males i.e. 51.9% females and 46.9% males. The mean baseline depression score was 10.62.

In Table 3 mean differences were calculated between two groups on the basis of study drugs i.e. citalopram and escitalopram by using independent sample t-test for week 12 and week 8 and Mann-Whitney *U* test for week 4.

Table 2
Baseline patients characterstics.

Characteristics	Total n = 80	Escitalopram n = 41	Citalopram n = 39
Age (years) (mean ± SD)	43.53 ± 11.1	44.26 ± 12.02	42.76 ± 10.14
Gender n (%) male	(38)47.5	(20)48.8	(18)46.2
Female	(42)52.5	(21)51.2	(21)53.8
Body weight (kg) (mean ± SD)	80. 4 ± 13.2	78.2 ± 13.0	83.4 ± 13.2
Baseline Depression score (mean ± SD)	10.62 ± 4.75	11.4 ± 5.26	9.76 ± 4.00

Table 3
Mean depression scores in escitalopram and citalopram group (during week 4, week 8 and week 12).

Treatment Duration	Citalopram Group N = 39 Mean ± SD	Escitalopram Group N = 41 Mean ± SD	Mean Difference (P-value)
Week 4	25.84 ± 5.08	26.51 ± 6.87	0.666 (0.836)
Week 8	19.43 ± 3.34	15.14 ± 4.87	4.28 (<0.001)[a]
Week 12	14.17 ± 3.01	10.41 ± 3.54	3.76 (<0.001) [a]

[a] Significant at 1%.

At week 4 the mean for citalopram was 25.84 and 26.51 for escitalopram. The mean difference was 0.666 with p value 0.836 that was not significant.

At week 8 the mean scores was 19.43 and 15.14 for citalopram and escitalopram respectively, with mean difference 4.28 and p value was calculated <0.001.

At week 12 and baseline the mean scores were 14.17 and 10.41 for citalopram and escitalopram respectively, with mean difference 3.76 and p value was calculated <0.001.

In Table 4 absolute mean differences were calculated between two study drugs i.e. citalopram and escitalopram. The mean for calculating difference in depression score between baseline and week 4 was 16.1 for citalopram and 15.0 for escitalopram, the mean difference was calculated 1.15 with p value 0.449.

The difference between depression score at week 8 and baseline was compared and the mean score was 9.74 and 3.63 for citalopram and escitalopram respectively, the mean difference was 6.10 and p value was calculated <0.001.

The difference between depression score at week 12 and baseline was compared and the mean scores were 4.48 and 1.09 for citalopram and escitalopram respectively, the mean difference was 5.58 and p value was calculated <0.001Fig. 2 [Fig. 2].

In Table 5 mean depression scores were calculated for baseline, week 4, week 8 and week 12 in citalopram and escitalopram group on the basis of gender.

The mean depression score for baseline in escitalopram group was calculated 10.4 for males and 12.5 for females with mean difference 2.17 and p value was 0.190. For depression score at week 4, the mean score value for males was 24.7 and 28.1 for females the mean difference

Table 4
Mean difference in depression scores from baseline to week 4, week 8 and week 12 between escitalopram and citalopram group.

Characteristics	Baseline & week 4	Baseline & week 8	Baseline & week 12
Citalopram	16.1 ± 6.34	9.74 ± 4.60	4.48 ± 4.41
Escitalopram	15.0 ± 7.17	3.63 ± 6.21	1.09 ± 5.66
Mean diff (p-value)	1.15 (0.449)	6.10 (<0.001)[a]	5.58 (<0.001)[a]

[a] Significant at 1%.

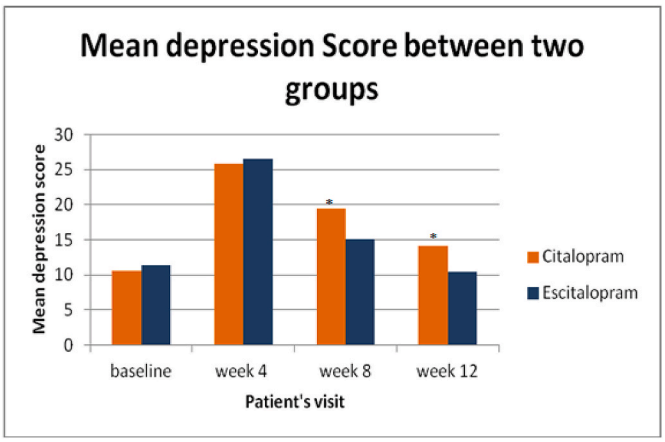


Fig. 2. Mean differences in depresion score among citalopram and escitalopram group at different visits.

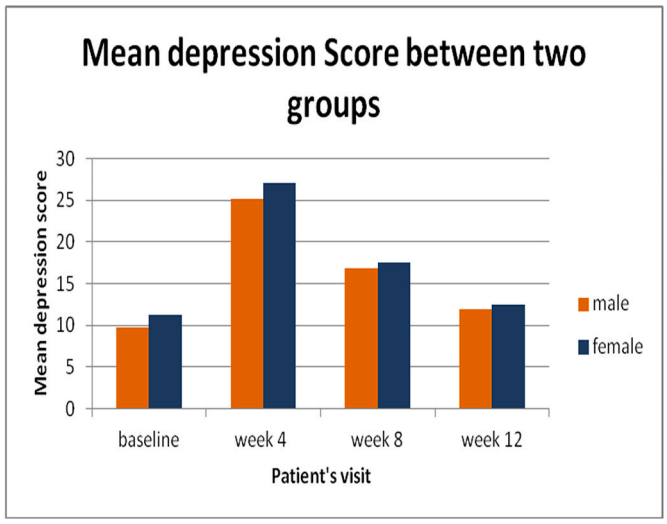


Fig. 3. Mean differences in depresion score among male and female patients at different visits receiving citalopram.

Table 5
Mean comparision of depression score between male and female patients in citalopram and escitalopram group (during baseline, week 4, week 8, and week 12).

Escitalopram Group:			
Treatment Duration	Escitalopram group Depression score in male Mean ± SD	Escitalopram group Depression score in female Mean ± SD	Mean Difference (P-value)
Baseline	10.4 ± 5.54	12.5 ± 4.87	2.17 (0.190)
Week 4	24.7 ± 5.7	28.1 ± 7.58	3.14 (0.110)
Week 8	15.8 ± 4.40	17.59 ± 4.96	0.653 (0.375)
Week 12	10.4 ± 3.48	10.4 ± 3.69	0.028 (0.980)
CITALOPRAM GROUP			
Treatment Duration	Citalopram group Depression score in male Mean ± SD	Citalopram group Depression score in females Mean ± SD	Mean Difference (P-value)
Baseline	9.11 ± 4.84	10.19 ± 3.15	1.07 (0.409)
Week 4	25.5 ± 4.03	26.1 ± 5.91	0.642 (0.699)
Week 8	14.2 ± 3.20	16.8 ± 4.40	0.70 (0.320)
Week 12	13.66 ± 2.80	14.6 ± 3.18	0.952 (0.332)

value was 3.14 with P value = 0.110.

At week 8, mean depression score for males was 15.8 and for females was 17.59 with the mean difference of 0.653 with P value = 0.375. Mean depression score for week 12 was 10.4 for males and 10.4 for females with a mean difference of 0.028 with P value = 0.980. P values for all variables were not significant.

The mean depression score for baseline in citalopram group was calculated as 9.11 for males and 10.19 for females with mean difference = 1.07 and P value = 0.409. For depression score at week 4 the mean for males was 25.5 and 26.1 for females with mean difference 0.642 and p value 0.669. At week 8th mean depression score for males was 14.2 and females was 16.8 with the mean difference of 0.70 with 0.320 p value. Mean depression score for week 12 was 13.66 for males and 14.6 for females with a mean difference 0.952 and 0.332 p value. P values for all variables were not significant [Fig. 3].

In Table 6 mean depression scores were calculated at baseline week 4, and week 12 on the basis of patient's age. The mean depression score at baseline was calculated 9.82 for patients ≤ 42 years and 11.42 for patients >42 years, with mean difference 1.60 and p value was 0.133. Mean depression score at week 4 for patients ≤ 42 years was 26.6 and 25.7 for patients >42 years with mean difference 0.825 and P value 0.544 Fig. 4.

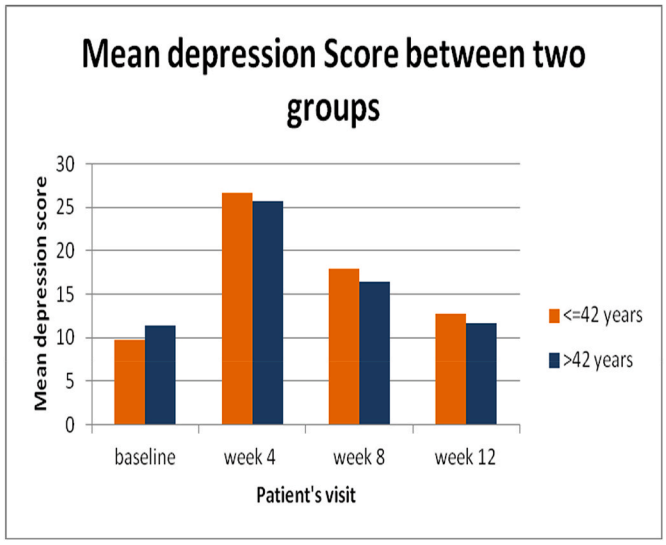


Fig. 4. Mean Differences In Depression Score In Patients On The Basis Of Age Key: 42 years is the mean age of patients.

Table 6
Mean comparision of depression score in different age groups (during baseline, week 4, week 8, and week 12).

Treatment Duration	Age ≤ 42 N = 40 Mean ± SD	Age>42 N = 40 Mean ± SD	Mean Difference (P-value)
Baseline	9.82 ± 4.87	11.42 ± 4.55	1.60 (0.133)
Week 4	26.6 ± 6.41	25.7 ± 5.68	0.825 (0.544)
Week 8	18.0 ± 5.31	16.4 ± 3.88	1.57 (0.135)
Week 12	12.7 ± 4.32	11.7 ± 3.14	0.950 (0.265)

Mean depression score at week 8 was calculated 18.0 for patients ≤ 42 years and 16.4 for patients >42 years with mean difference of 1.57 with P value = 0.135. Mean depression score at week 12 was 12.7 for patients ≤ 42 years and 11.7 for patients>42 years with a mean difference 0.950 and P value = 0.265. P values for all variables were not significant.

4. Discussion

In this clinical trial two antidepressant drugs citalopram and escitalopram of same class, selective serotonin reuptake inhibitors (SSRIs) are compared in Pakistani population in Hepatitis C patients.

This study shows better efficacy of escitalopram in the treatment of depression that is caused by interferon therapy in Hepatitis patients than citalopram, its parent compound. The mean differences calculated for depression were supporting escitalopram. The mean change in depression score at the end of the study was greater in escitalopram group i.e.10.41 as compared to citalopram group i.e.14.17 with p value <0.001 that is significant.

The absolute mean differences between groups were also calculated. The difference in depression score between baseline and week 4 was not significant. The difference in depression score between week 8 and baseline and, week 12 and baseline was significant that shows that depression scores after therapy with antidepressants reduced the depression score. The depression score was greatly reduced in escitalopram group as compared to citalopram group.

Some previous studies were also persistent with our results. Montgomery, S.A., et al. analyzed in a double blind, randomized trial in primary care patients that escitalopram is efficacious in depression and the effect occurs earlier than citalopram [23].

Kasper, S., et al. also explained superior efficacy of escitalopram on the basis of occupancy of serotonin reuptake transporter [24].

Davis, G.L., et al. Gleason, O.C., W.R. Yates, and M.A. Philipsen in their studies also supported escitalopram over citalopram in higher response rates [25].

Yevtushenko, V.Y., et al. also demonstrated the efficacy of escitalopram in randomized double blind study and found that escitalopram is more effective than citalopram in treating depression [26].

Montgomery et al. and Lepola et al. also supported our results by reviewed different randomized trials. They found 3 antidepressants to have possible superiority, but at the end they found esciatopram is only antidepresssnt with distinct superiority in treating severe depression [27,28].

Kasper S et al. also found escitalopram more efficacious and tolerable in treatment of generalized anxiety disorder as compared to other SSRIs [29,30].

Lam, R.W. and L. Annemans, Llorca, P.M. et al. also validated the benefits of escitalopram compared with citalopram in terms of significance and onset of action [31,32].

In current study the mean differences calculated for escitalopram and citalopram showed significant results. The difference in depression score was calculated at week 12 ($P < 0.001$), that is significant.

Our results showed better tolerability of escitalopram than other SSRIs and is also supported by results of Lalit, V., et al. In double blind trial that escitalopram is better tolerated than sertraline and citalopram and is more safe and efficacious than other antidepressants of same class [33].

Schaefer, M., et al. also revealed that preemptive escitalopram shows better results in interferon associated depression in hepatitis C virus infected patients [34].

However different previous studies are not in favor of current study, Trkulja, V. demonstrated that escitalopram superiority over citalopram is not significant in short to medium treatment of depression [35].

Ou et al. also found that citalopram is equally efficacious as escitalopram in treating depression among Chinese population [36].

Absolute mean differences were also calculated for citalopram and escitalopram on the basis of gender. The results calculated were not significant in current study that proves that depression is not specific for gender. Depression by interferon can develop in both male and female at the same ratio. Another study by Martin-Santcos supported our findings because they also did not found any differences in depression score on the basis of gender in their study [37].

Mean differences in depression score on the basis of age was also calculated by dividing the patients into 2 age groups i.e. $<=42$ years and >42 years. Because the mean age of patients was 42. The results exhibited no significant differences between two groups that show that there is no effect of age on development of depression during interferon therapy.

The limitation of the study is that more test centers could be added that would be more interesting. Sample size of the study may be increased. One new group as placebo could be added. Hemolytic anemia could be caused by Ribavirin.

5. Conclusion

In conclusion, in this double blind, randomized trial of interferon induced depressed Hepatitis C patients, escitalopram proved greater efficacy in reducing depression from baseline to the end of the study than its parent compound, as assessed by using AKUADS depression scale. Also different parameters compared at the end of the study confirmed the superiority of escitalopram over citalopram. Escitalopram is far better in reducing adverse events associated with depression.

The suggested mechanism of action of escitalopram may explain its improved efficacy compared with other SSRIs.

Disclaimer

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Funding disclosure

None to declare.

Declaration of competing interest

None to declare.

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