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Original Research Article

# Study of Efficacy, Remission and Tolerability of Fluoxetine Versus Desvenlafaxine in Patients with Depression in a Tertiary Care Hospital: An Open Labelled Randomized Interventional Comparative Study

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**Conflict of interest: Nil**

**Abstract:**

**Introduction:** Depression is a common psychiatric disorder affecting both the mind and body. It is a severe, recurrent and disabling medical illness. It is the third leading cause of global disease burden and could become the leading cause by 2030 if not detected and treated early. Antidepressants are the mainstay of treatment of which SSRIs and SNRIs are frequently used.

**Objectives:** To compare the efficacy, remission and tolerability of fluoxetine with desvenlafaxine.

**Materials and Methods:** An open labelled, randomized, interventional, comparative parallel design study was conducted in patients with depression. One hundred patients included in the study were randomized into 2 groups of 50 each. Group A patients were given desvenlafaxine(50-100mg/day) orally for 8 weeks while Group B patients received fluoxetine (20-60mg/day) orally for 8 weeks. Patients were followed up every 2 weeks for 8 weeks. Efficacy & remission rate of both drugs were assessed using CGI scores. Tolerability was evaluated by the number of adverse effects experienced by each patient. Data collected was analysed statistically. Findings were noted.

**Results:** Early improvement at 2weeks in Group A and Group B by CGI-S was 24% and 8.2%, by CGI-I was 22% and 0.5% respectively. Efficacy was 76.8% and 73% in Group A by CGI-S and CGI-I respectively while in Group B it was 70.5% and 68% respectively. Remission in Group A and Group B by CGI-S score was 86% and 68%, by CGI-I score was 94% and 72%, by CGI-E was 94% and 70% respectively. All these were statistically significant between and within the groups. Tolerability was comparable in both groups where in Group A showed 48% excellent and 38% good tolerability, Group B showed 46% excellent and 36% good tolerability. Remaining showed fair tolerability.

**Conclusion:** Desvenlafaxine showed statistically significant early improvement, efficacy and remission rate compared to fluoxetine. Tolerability profile between the groups was comparable. Desvenlafaxine can be used to treat depression.

**Keywords:** Depression, Fluoxetine, Desvenlafaxine, Efficacy, Remission, Tolerability.



## Introduction

Depression is a mood disorder characterized by sadness, fatigue, low self- esteem, guilt feelings, gastrointestinal disturbances, suicidal thoughts and decreased energy, sleep, sexual interest and motivation.[1] It affects the mental well- being, functioning and quality of life of the individual and economy of family and society.[2]

According to World mental health survey 10-15% of the people suffer from depression in their lifetime.[3] Global prevalence is 5.8% in females and 3.5% in males.[4] One year prevalence is 15.9% in an Indian study.[5]

There are various modalities of depression treatment of which the most common is antidepressant medication.[6] SSRIs (Selective Serotonin Reuptake Inhibitors) and SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors) are the most commonly prescribed antidepressants because of their safety and efficacy compared to older drugs. Among SSRIs fluoxetine is one of the commonly used drugs which has a slower onset of action compared to venlafaxine and is safer in

children. It's adverse effects are nausea, diarrhoea, headache, insomnia, irritability, erectile dysfunction, loss of orgasm, delayed ejaculation, serotonin syndrome and decreased concentration. It has more interactions due to inhibition of cytochrome enzymes.[7]

Desvenlafaxine, FDA approved third SNRI, a metabolite of Venlafaxine has a serotonin to norepinephrine inhibition ratio of 11.[8] It has less interactions as it is metabolised only by cytochrome enzyme CYP3A4. It's adverse effects are nausea, headache, dizziness, dry mouth, constipation, insomnia, decreased appetite, hyperhidrosis, fatigue, abdominal pain and anxiety.[9]

Studies have shown that venlafaxine has early onset of action and more efficacy but with lesser safety profile compared to Fluoxetine. Desvenlafaxine has similar efficacy but lesser interactions compared to venlafaxine. No study has been done to compare the efficacy, remission and tolerability of fluoxetine with desvenlafaxine, prior to conduction of my study. Hence this study was conducted in a tertiary care hospital. Later very few studies have been conducted.

## Materials and Methods

### Study Design

An open labelled, randomized, interventional, comparative parallel design study was conducted by the Department of Pharmacology in association with Department of Psychiatry in a tertiary care hospital, from January 2014 to March 2015.

### Inclusion Criteria

Patients attending OPD (Out Patient Department) of Psychiatry department, newly diagnosed with moderate and severe depression without psychosis as per ICD-10 (International Classification of Diseases Tenth Revision) criteria of either sex aged 18-60 years.

### Exclusion Criteria

Pregnant women, lactating mothers, patients with history of hypothyroidism, hypertension, diabetes mellitus, pulmonary tuberculosis, leprosy, HIV–AIDS, cancer, cardiac disease, hepatic disease and renal disease were excluded from the study.

### Method

Ethical clearance from institutional ethics committee was obtained prior to conduct of study. 100 patients diagnosed with depression were enrolled in the study after applying inclusion-exclusion criteria.

A detailed history was recorded and a thorough clinical examination by a qualified psychiatrist was performed at the start of the study. Patients were screened by subjecting them to required investigations. An informed written consent was taken from them. Selected patients were divided into two groups of 50 each by block randomization. Group A patients received desvenlafaxine orally once daily for 8 weeks with 50mg at start, later 100mg if there was no relief from symptoms at 2 weeks; while Group B received fluoxetine once daily, orally for 8 weeks with 20mg at start, later increased to 40mg at 2 weeks then 60mg at 4 weeks if relief from symptoms was not noticed. Follow up was done once in 2 weeks for 8 weeks. Required investigations and periodic psychiatric assessment for efficacy, remission and tolerability of both antidepressants were done at each follow up till the end of study by a qualified psychiatrist along with repeated contact through calls and counselling which helped in regular follow up. Investigations done at baseline were complete blood count, random blood glucose, serum cholesterol and triglycerides, liver function tests, blood urea, serum creatinine, TSH levels, ECG, blood pressure and body weight measurements. All these investigations except TSH levels were repeated at the end of study. Complete blood count, blood pressure and body weight measurements were done at the end of 2, 4, & 6 weeks.

### Assessment scores

Early improvement was evaluated by measuring the mean reduction in CGI (Clinical Global Impression) score at the end of 2 weeks by giving scores ranging from 1-7 for CGI-S (CGI-Severity) and CGI-I (CGI Improvement) scores. Efficacy was assessed by measuring the reduction in scores at the end of the study from baseline scores. Remission rate was evaluated by calculating the percentage of patients with CGI-S of 1 (normal, not at all ill), CGI-I of 1(very much improved) and CGI-E (CGI Efficacy index) of 1 (marked improvement, no side effect). Tolerability was assessed by the number of adverse effects experienced by each patient in both groups and accordingly graded as Excellent (No adverse effects), Good (1-2 adverse effects), Fair (3-4 adverse effects) and Poor (5 or more adverse effects).

### Statistical Analysis

Results were analysed using SPSS 21. Mean ± standard deviation, percentage were calculated. Using independent t test and chi square test, p value was calculated and it's value <0.05 was considered as statistically significant.

## Results

Out of 100 patients selected for the study, 41 were males and 59 were females. 48 patients were in age group of 18-30 years, followed by 31 in 31-40 years of age, 10 were 41-50 years and 11 were 51-

60 years of age. Patient drop out from study was nil.

Both the groups were comparable with respect to age, sex and baseline investigation values.

Early improvement in Group A at 2 weeks by CGI severity score was 24% with a mean reduction of 1.22±0.5 from 5.08±0.8 at baseline. Early improvement at 2 weeks by CGI-I score was 22% with a mean difference of 0.88±0.02 from 4.00 at baseline and in Group B by CGI-S Severity Score was 8.2% at 2 weeks with a mean difference of 0.38±0.3 from 4.68±0.3 at baseline; whereas, by CGI-I score was 0.5% with a mean difference of 0.02 ±0.1 at 2 weeks from 4.00 at baseline. Early improvement by both scores were statistically significant. (See Table 1& 2).

Efficacy rate in Group A by CGI-S was 76.8% with a mean reduction of 3.90±0.7 from 5.08±0.8 at baseline and by CGI-I score they were 73.5% and 2.94±0.2 (from 4.00 at baseline) respectively whereas efficacy rate in Group B by CGI-S was 70.5%, mean score reduction was 3.30±0 from 4.68±0.3 at baseline; and by CGI-I score they were 68% and 2.72±0.2 (from 4.00 at baseline) respectively and were statistically significant. CGI-E score at the end of study was 1.24±0.9 in Group A and 2.20±1.8 in Group B and was statistically significant (p=0.002). (See Table 1, 2, 3, 4 and Fig 1 & 2).

Remission at the end of study in Group A by CGI-S score was seen in 43 patients (86%), by CGI-I and CGI-E individually was 94%. In Group B by CGI-S score was 68%, by CGI-I was 72% and by CGI-E was 70% and were statistically significant with p value =0.03 in CGI-S, p= 0.003 in CGI-I and p=0.001 in CGI-E. (See Fig 3).

**Tolerability**

In Group A and Group B 24 and 23 patients showed excellent tolerability, 19 and 16 patients showed good tolerability, 07 and 09 patients showed Fair tolerability respectively. Poor tolerability was not seen in both the groups. There was no statistical significance in tolerability between the groups. (Table 5 and Fig 4). All investigations between the groups were comparable and not statistically significant. ECG at the start and at the end of study of all patients in both groups was within normal limits.

**Table 1: Comparison of Clinical Global Impression Scores at Different Weeks**

| Time | Clinical Global Impression-Severity Scores | | | Clinical Global Impression-Improvement Scores | | |
|---|---|---|---|---|---|---|
| | Group A (n=50) (mean score ± Sd) | Group B (n=50) (mean score ± Sd) | p value* | Group A (n=50) (mean score ± Sd) | Group B (n=50) (mean score ± Sd) | p value* |
| Baseline | 5.08+/-0.8 | 4.68+/-0.3 | 0.54 | 4.00 | 4.00 | 1 |
| 2weeks | 3.86+/-0.9 | 4.30+/-0.7 | 0.001 | 3.12+/-0.1 | 3.98+/-0.2 | 0.002 |
| 4weeks | 2.62+/-0.6 | 3.20+/-0.6 | 0.001 | 2.14+/-0.3 | 2.86+/-0.3 | 0.001 |
| 6weeks | 1.88+/-0.3 | 2.18+/-0.4 | 0.001 | 1.72+/-0.4 | 2.00+/-0.0 | 0.001 |
| 8weeks | 1.18+/-0.3 | 1.38+/-0.4 | 0.02 | 1.06+/-0.2 | 1.28+/-0.4 | 0.003 |

*Independent t test, Sd- Standard deviation

**Table 2: Comparison of mean differences in Clinical Global Impression Scores at different intervals**

| Duration | Clinical Global Impression-Severity Scores | | | Clinical Global Impression-Improvement Scores | | |
|---|---|---|---|---|---|---|
| | Group A (n=50) (mean score ± Sd) | Group B (n=50) (mean score ± Sd) | p value* | Group A (n=50) (mean score ± Sd) | Group B (n=50) (mean score ± Sd) | p value* |
| 0 - 2weeks | 1.22+/-0.5 | 0.38+/-0.3 | 0.001 | 0.88+/-.02 | 0.02+/-0.1 | 0.04 |
| 0 -4weeks | 2.46+/-0.5 | 1.48+/-0.4 | 0.002 | 1.86+/-0.1 | 1.14+/-0.1 | 0.001 |
| 0 - 6weeks | 3.20+/-0.7 | 2.50+/-0.8 | 0.431 | 2.28+/-0.5 | 2.00+/-0.4 | 0.001 |
| 0 - 8weeks | 3.90+/-0.7 | 3.30+/-0.1 | 0.001 | 2.94+/-0.2 | 2.72+/-0.2 | 0.001 |

*Independent t test, Sd- Standard deviation

**Table 3: Comparison of Efficacy Rate in Clinical Global Impression Scores at different intervals**

| Duration | Efficacy Rate By CGI-S Score | | | Efficacy Rate by CGI-I Score | | |
|---|---|---|---|---|---|---|
| | Group A | Group B | p value* | Group A | Group B | p value* |
| 0 - 2weeks | 24% | 8.20% | 0.001 | 22% | 0.50% | 0.04 |
| 0 -4weeks | 48.60% | 31.60% | 0.002 | 46.50% | 28.50% | 0.001 |
| 0 - 6weeks | 63.60% | 53.40% | 0.431 | 57% | 50% | 0.001 |
| 0 - 8weeks | 76.80% | 70.50% | 0.001 | 73.50% | 68% | 0.001 |

*Independent t test, Sd- Standard deviation

**Table 4: Comparison of Clinical Global Impression-Efficacy Index at Different Weeks**

| Time | Group A (n=50) (mean score +/Sd) | Group B (n=50) (mean score +/Sd) | p value* |
|---|---|---|---|
| 2 weeks | 9.98+/-1.5 | 12.74+/-1.5 | 0.001 |
| 4 weeks | 6.00 +/-1.5 | 8.76+/-1.4 | 0.001 |
| 6 weeks | 3.88+/-1.8 | 5.00+/-0.0 | 0.001 |
| 8 weeks | 1.24+/-0.9 | 2.20+/-1.8 | 0.002 |

*Independent t test, Sd- Standard deviation

**Table 5: Comparison of Tolerability of Desvenlafaxine and Fluoxetine in Study Groups**

| | Groups | |
|---|---|---|
| **Number of Adverse effects** | **Desvenlafaxine** | **Fluoxetine** |
| | (Group A) | (Group B) |
| Excellent (Nil) | 24 (48%) | 23 (46%) |
| Good (1–2) | 19 (38%) | 18 (36%) |
| Fair (3–4) | 07 (14%) | 09 (18%) |
| Total | 50 (100%) | 50 (100%) |

Chi square value: 0.298 df-2, p value: 0.86

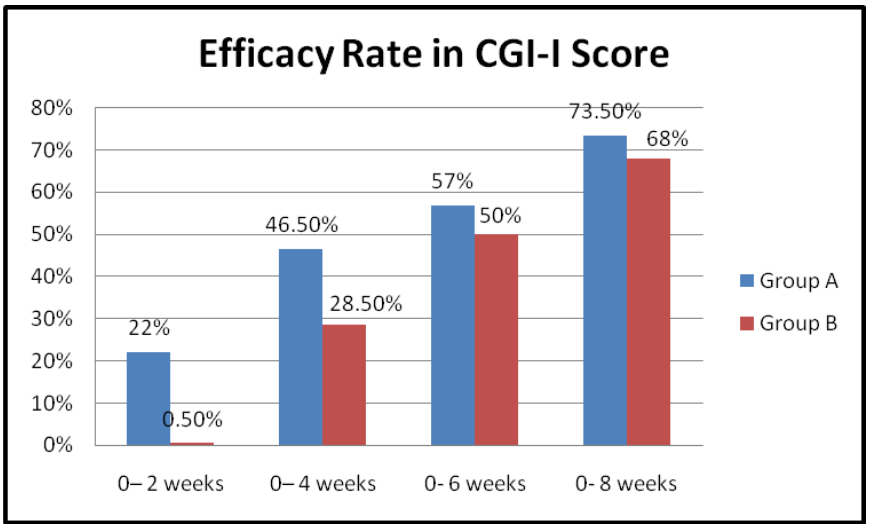


**Figure 1: Efficacy Rate in Clinical Global Impression –Improvement score at different Weeks**

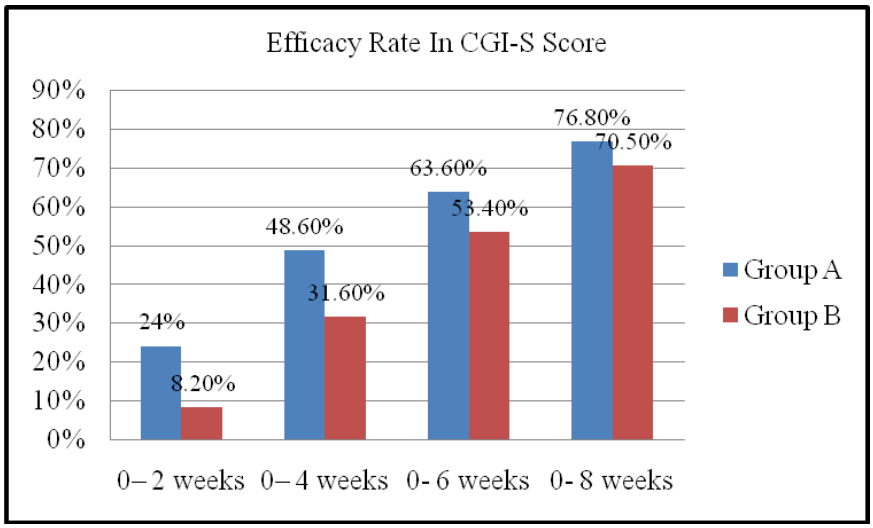


**Figure 2: Efficacy Rate in Clinical Global Impression –Severity score at different weeks**

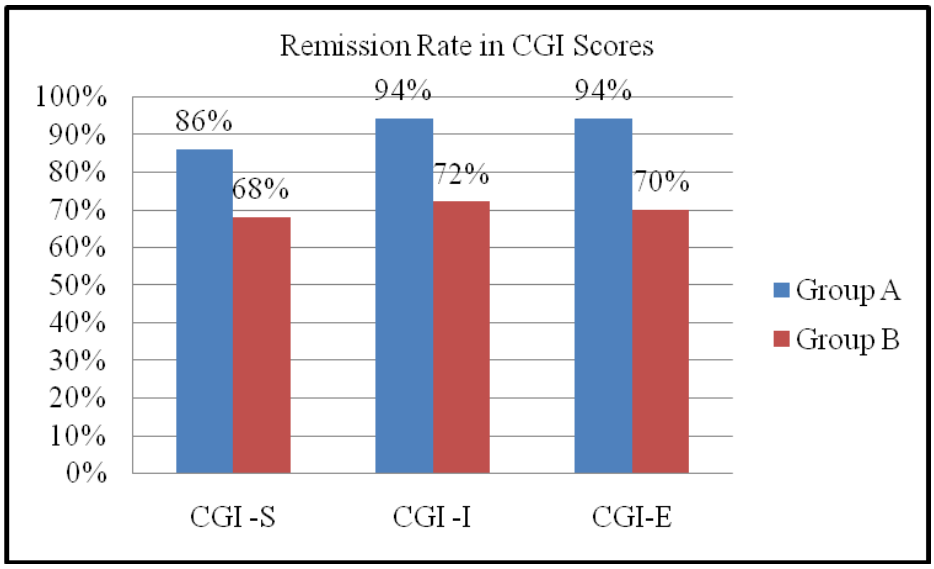


**Figure 3: Remission Rate in Clinical Global impression-severity (CGI-S), Clinical Global Impression - Improvement (CGI-I), Clinical Global impression-efficacy index (CGI-E) scores at the end of the study**

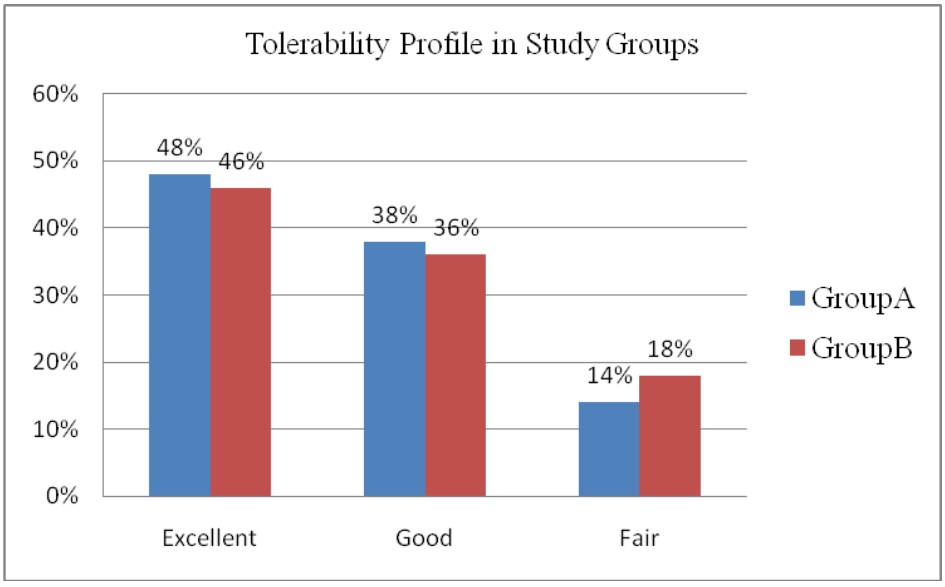


**Figure 4:Tolerability profile in study groups at the end of 8weeks**

## Discussion

SNRIs and SSRIs show better improvement in depression symptoms due to their better efficacy and tolerability compared to older antidepressants.[10] Desvenlafaxine causes higher inhibition of NET (norepinephrine reuptake transporter) and has less cytochrome enzyme inhibition than venlafaxine. A study has shown that decreased pharmacokinetic variation could give better response with desvenlafaxine than venlafaxine.

Goal of treatment of depression is remission of all symptoms. About 30-40% of patients achieve remission. Antidepressant medication should be continued for 6-12 months after remission to reduce chances of relapse. [11,12]

Study has shown that depression is most common in 20-40 years of age [2] which is similar to that in our study of 79% in 18-40 years of age. Another study showed that depression was more in females (64%) compared to males (36%) [13] and is almost similar to that in our study, which could be due to stress, socioeconomic conditions and cultural practices.

A meta-analysis study of desvenlafaxine versus placebo showed a significant change in CGI-I and CGI-S scores from 2nd week onwards which is comparable to our study with desvenlafaxine versus fluoxetine.[14] Studies have shown significant early clinical improvement in CGI scores after 2 weeks by venlafaxine compared to fluoxetine and is comparable to that in our study but with desvenlafaxine instead of venlafaxine. This suggests that a rapid onset with venlafaxine or desvenlafaxine could be due to pharmacodynamic properties of these drugs. Early improvement in depression symptoms may result in better patient

compliance and outcome. [15,16, 17]

A study has shown that there was a significant difference in CGI-I and CGI-S scores at the end of study. CGI-I score was 2.9 in placebo and 2.5 in desvenlafaxine group (p= 0.0371) while CGI-S reduction was 0.9 in placebo and 1.2 in desvenlafaxine group (p= 0.041) [10] while in our study though they were statistically significant for desvenlafaxine versus fluoxetine, the scores were greatly reduced, and their differences were more compared to this study.

Statistical significance in CGI scores was seen with desvenlafaxine versus placebo at the end of the studies which is similar to that in our study but with fluoxetine instead of placebo. [14,18,19]

Studies have shown that there was no statistical significance in CGI scores for desvenlafaxine versus placebo [9,20] versus fluoxetine [20] which is not in comparison with our study.

Studies have shown a statistical significance in efficacy on CGI-I and CGI-S scores for venlafaxine versus fluoxetine where in p value was ≤ 0.019[16,21]; whereas in our study (desvenlafaxine versus fluoxetine) p = 0.001 and for CGI-E p= 0.002.

37.1% in venlafaxine group and 52.9% in fluoxetine group required increase in dose at 2 weeks of treatment whereas in our study it was 10% in fluoxetine group and 2% in desvenlafaxine group.[16]

Remission is a measurement of efficacy. [16,21] In all studies remission was achieved if CGI scores at the end of study was 1. In a study remission by CGI-I score was 51% in venlafaxine group as compared to 32% in fluoxetine group (p=0.0018) [21] while in our study it was 94% with desvenlafaxine and 72% with fluoxetine (p= 0.003).

Treatment acceptability is reflected by adverse effects and patient drop- out rate due to adverse effects is an indicator of tolerability. Adverse effects were frequent in 1st week of treatment which is comparable to our study.[22] Discontinuation due to adverse effects of desvenlafaxine was similar to placebo (4 %); [14,22] while in another study it was 27%,19% and 9% with venlafaxine, fluoxetine and placebo respectively. At least one adverse effect was experienced by 92%, 94% and 82% patients with venlafaxine, fluoxetine and placebo respectively.[20]

In a study, fewer patients in venlafaxine group discontinued treatment as compared to fluoxetine. 55.7% in venlafaxine and 67.1% in fluoxetine group experienced at least one adverse effect.[16] In another study it was 85% with desvenlafaxine and 91% with venlafaxine.[23] In our study it was 52% with desvenlafaxine and 54% with fluoxetine. 9% in desvenlafaxine and 16% in venlafaxine group discontinued treatment due to adverse effects.[23] Patient drop out was not seen in our study.

In a study by Alan Schatzberg.et.al.,[20] 45% and 26% of patients in venlafaxine group experienced nausea and headache respectively, while in fluoxetine group they were 23% and 18% respectively. In another study, nausea rate was 27% and 38% in desvenlafaxine and venlafaxine group respectively.[23] Whereas in our study headache was experienced by 18% patients on desvenlafaxine as compared to 20% on fluoxetine and nausea was 16% in both the groups. From the above studies and our study, it is evident that desvenlafaxine has a better early improvement, efficacy, remission and tolerability compared to placebo, venlafaxine and fluoxetine.

## Conclusion

Our study showed statistical significance in early improvement of symptoms, efficacy and remission rate by desvenlafaxine compared to fluoxetine. Both the drugs had similar tolerability profile. Hence desvenlafaxine can be considered to treat moderate and severe depression without psychosis excluding those having comorbid conditions.

**Limitations of the study:** As the study was a mono centred, open labelled and conducted on a small sample size for a shorter duration the results cannot be generalized to the whole population from which the patients were selected. Bias might be present, also long term efficacy, remission and tolerability profile of both the drugs were not evaluated. Multi-centric clinical studies comparing both these drugs on a larger sample size for a longer duration of study and also on depression patients with comorbid conditions are recommended.

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