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Original research article

Vilazodone with escitalopram in patients of major depressive disorder: Comparison of clinical profile

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Abstract

Vilazodone is a partial agonist at the 5HT1A receptor and also inhibits serotonin reuptake; thus, it is referred to as a serotonin partial agonist/reuptake inhibitor (SPARI). Its effects at 5HT1A receptors are equal to or more potent than its effects at serotonin transporters. A prospective, randomized, active-controlled, parallel-group comparative open label study was conducted on total 92 patients of major depressive disorder at psychiatry OPD, meeting inclusion criteria. Diagnosis of patient as a patient of major depressive disorder was done by psychiatrist. A written informed consent from the patient or legal guardian of patient was taken after explaining nature and purpose of study in their own language. Patient information sheet containing all the necessary details of study was provided to patient. Patients who were selected for Vilazodone were found to have mean systolic BP of 113.00±15.45 mmHg, and patients belonging to Escitalopram were having 114.08±6.00 respectively. There was no statistically significant difference between two groups (P value 0.658). Patients who were selected for Vilazodone were found to have mean diastolic BP ± S.D. of 78.26±16.21, and patients belonging to Escitalopram were having 74.52±4.88 respectively. There was no statistically significant difference between two groups (P value 0.138).

Keywords: Vilazodone, escitalopram, major depressive disorder

Introduction

Major depressive disorder (MDD) is a serious chronic and recurrent psychiatric illness, and accounts for 10%-14% of all patients seen by primary care physicians. The cardinal symptoms of MDD include diminished pleasure or interest in daily activities, changes in appetite or weight, sleep disorders, difficulty concentrating, fatigue, psychomotor agitation, sad mood, feelings of worthlessness, and even suicidal thoughts. These symptoms lasting for period of 2 week. The symptoms may also be accompanied by complaints of anxiety by patients, somatic complaints such as bodily aches, pains and irritability [1].

Vilazodone is a partial agonist at the 5HT1A receptor and also inhibits serotonin reuptake; thus, it is referred to as a serotonin partial agonist/reuptake inhibitor (SPARI). Its effects at 5HT1A receptors are equal to or more potent than its effects at serotonin transporters [2].

Vilazodone is absorbed in the gastrointestinal tract and reaches peak concentration at a median of 4 to 5 hours. Its bioavailability increases when taken with food such that Cmax (maximum concentration) is increased by 147% to 160%, and area under the curve is increased by 64% to 85%. Its absolute bioavailability in the presence of food is 72%. In systemic circulation, the drug is 96% to 99% protein-bound. Vilazodone is eliminated primarily through cytochrome P450 (CYP) 3A4 metabolism in the liver. Terminal half-life of Vilazodone is 25 hours. In general, steady state is achieved in 4 to 5 times the half-life at a stable dose. However, dosing guidelines for Vilazodone recommend titration over 2 weeks to achieve a target of 40 mg/d. Thus, steady state will not be achieved until the patient has been on the stable target dose for approximately 2.5 weeks [3].

Vilazodone is contraindicated for concomitant use with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping or starting an MAOI. Vilazodone is contra-indicated in patients taking strong CYP3A4 inhibitors (e.g., ketoconazole) because of increased Vilazodone concentrations and resulting concentration-dependent adverse effects. Concomitant administration of strong CYP3A4 inducers (e.g., rifampin) might result in a reduction in Vilazodone levels leading to lack or loss of efficacy [5].

As with other antidepressants, Vilazodone carries a black-box warning about increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for MDD and

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other psychiatric disorders. Vilazodone showed evidence of developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate, well-controlled studies of Vilazodone in pregnant women and no human data regarding Vilazodone concentrations in breast milk. Women taking Vilazodone are advised to breast-feed only if the potential benefits outweigh the risks. Vilazodone is not recommended for use in pediatric patients [6].
Similar to other antidepressants, Vilazodone labeling carries warnings about serotonin syndrome, seizures, abnormal bleeding, activation of mania/hypomania and hyponatremia.

Methodology
A prospective, randomized, active-controlled, parallel-group comparative open label study was conducted on total 92 patients of major depressive disorder at psychiatry OPD, meeting inclusion criteria after approval of Institutional Ethics Committee.
Diagnosis of patient as a patient of major depressive disorder was done by psychiatrist. A written informed consent from the patient or legal guardian of patient was taken after explaining nature and purpose of study in their own language. Patient information sheet containing all the necessary details of study was provided to patient. Eligible patients were randomized using block permutation method with allocation ratio of 1:1 to receive either Escitalopram or Vilazodone. Patient receiving Escitalopram was considered as control (C) group and vilazodone as experimental (E) group. Good Clinical Practice (GCP) guidelines were strictly followed.

Study setting: The present study was carried out in psychiatry OPD of tertiary care hospital.
Study design: A prospective randomized, active controlled, parallel-group, comparative, open-label study.
Study population: All patients of either sex who attended psychiatry outdoor clinic with clinical diagnosis of MDD as per the diagnostic and statistical manual of mental disorder, fifth edition (DSM-V).

Inclusion criteria
1. Patients of either sex with age between 18 to 65 years.
2. Newly diagnosed MDD patients meeting DSM 5 criteria for depression.
3. Patient who give written informed consent.

Exclusion criteria
1. Pregnant or nursing women.
2. Patients with high risk of suicidal tendency or previous suicide attempt within 6 months.
3. Patients with bipolar disorder, drug abuse or dependency, post-traumatic stress disorder, obsessive-compulsive disorder.
4. Patients with previous depression resistant to antidepressants and those who had taken treatment with electroconvulsive therapy in previous 3 months or formal psychotherapy within 1 month.
5. Patients on other antidepressants.
6. Patients with neurological disorders (dementia, seizures, stroke), obesity with functional impairment, serious or unstable organic disorder (neoplasia, cardiovascular, Pulmonary, uncontrolled type 1 or 2 diabetes).
7. Any other medical disorder which is confounding our inclusion diagnosis.
8. Patients with drug intake for psychosis or anxiety.
9. Any history of allergy to the drugs.

Patient's details were taken on a proforma, including patients age, sex, occupation, religion, marital status, type of family, total family members, total income, per capita income, socio-economic class (by B.G. Prasad classification), history of any medical illness, duration and treatment received for the same was recorded. Family h/o any psychiatric disorder was also taken. Also patient's weight, BP, was recorded. Weight of patient was taken on a same type digital weighing machine throughout the study. BP of patient was recorded with same type of sphygmomanometer till the end of study. CBC, serum creatinine, serum urea, liver function tests were done, at baseline (day 1), 4th week, and at 12 weeks at the same institution with same method.

Results

Table 1: Comparison of Blood pressure in two groups studied

Variables	Treatment Received		Total	P Value
	Group C	Group E		
SBP	114.08±6.00	113.00±15.45	113.54±11.67	0.658
DBP	74.52±4.88	78.26±16.21	76.39±12.05	0.138

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As shown in table patients who were selected for Vilazodone were found to have mean systolic BP of 113.00±15.45 mmHg, and patients belonging to Escitalopram were having 114.08± 6.00 respectively. There was no statistically significant difference between two groups (P value 0.658).
Patients who were selected for Vilazodone were found to have mean diastolic BP ± S. D. of 78.26±16.21, and patients belonging to Escitalopram were having 74.52±4.88 respectively. There was no statistically significant difference between two groups (P value 0.138).

Table 2: Comparison of serum creatinine in two groups studied

Serum creatinine	Treatment Received		Total	P Value
	Group C	Group E		
LFT_BASELINE	0.86±0.29	0.84±0.30	0.85±0.29	0.650
LFT_4THWEEK	0.82±0.14	1.12±1.90	0.97±1.35	0.298
LFT_12THWEEK	0.83±0.39	1.11±1.71	0.97±1.25	0.287

As shown in table patients who were selected for Vilazodone were found to have mean baseline serum creatinine of 0.84±0.30, and it was 1.12±1.90 and 1.11±1.71 at 4 and at 12 weeks, respectively. While patients who were selected for Escitalopram were having mean baseline serum creatinine of 0.86±0.29 at 4 and at 12 weeks; it was 0.82±0.14 and 0.83±0.39, respectively. It was found that there was no statistically significant change in serum creatinine values in both groups.

Table 3: Comparison of serum Urea in two groups studied

Serum Urea	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	26.51±6.07	27.66±7.49	27.07±6.79	0.418
4th Week	26.97±6.44	27.47±7.98	27.22±7.20	0.744
12th Week	26.89±6.86	27.43±8.62	27.15±7.73	0.742

As shown in table patients who were selected for Vilazodone were found to have mean baseline serum urea ± S. D. of 27.66±7.49 and it was 27.47±7.98 and 27.43±8.62 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline serum urea of 26.51±6.07 at 4 and at 12 weeks; it was 26.97±6.44 and 26.89±6.86, respectively. It was found that there was no statistically significant change in serum creatinine values in both groups.

Table 4: SGOT-A Comparison in two groups studied

SGOT	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	32.25±18.66	30.80±4.67	31.54±13.68	0.613
4th Week	33.19±18.69	31.29±5.13	32.26±13.79	0.517
12th Week	32.83±18.73	31.34±5.40	32.10±13.85	0.611

As shown in table patients who were selected for Vilazodone were found to have mean baseline serum SGOT ± S.D. of 30.80±4.67 and it was 31.29±5.13 and 31.34±5.40 at 4 and at 12 weeks, respectively. While patients who were selected for Escitalopram were having mean baseline serum SGOT of 32.25±18.66 at 4 and at 12 weeks; it was 33.19±18.69 and 32.83±18.73, respectively. It was found that there was no statistically significant change in serum SGOT-A values in both groups.

Table 5: SGPT-A Comparison in two groups studied

SGPT	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	21.46±10.06	24.06±14.02	22.73±12.16	0.308
4th Week	21.43±10.24	23.30±14.01	22.33±12.17	0.472
12th Week	21.22±10.22	213.45±14.37	22.31±12.40	0.397

In our study we found that patients who were selected for Vilazodone were found to have mean baseline serum SGPT ± S. D. of 24.06±14.02, and it was 23.30±14.01 and 213.45±14.37 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline serum SGPT of 21.46±10.06 at 4 and at 12 weeks; it was 21.43±10.24 and 21.22±10.22, respectively. It was found that there was no statistically significant change in serum SGPT values in both groups.

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Table 6: ALP-A Comparison in two groups studied

ALP	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	88.94±21.60	83.08±17.66	86.08±19.88	0.159
4th Week	87.28±21.51	84.25±14.54	85.80±18.39	0.439
12th Week	87.00±21.06	83.91±14.63	85.49±18.17	0.424

Table show that patients who were selected for Vilazodone were found to have mean baseline serum ALP± S.D. of 83.08±17.66, and it was 84.25±14.54 and 83.91±14.63 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline serum ALP of 88.94±21.60 at 4 and at 12 weeks; it was 87.28±21.51 and 87.00±21.06, respectively. It was found that there was no statistically significant change in serum ALP values in both groups.

Table 7: Direct Bilirubin-A Comparison in two groups studied

Direct Bilirubin	Treatment Received		Total	P Value
	Group C	Group E		
LFT_BASELINE	0.24±0.17	0.18±0.06	0.21±0.13	0.019*
LFT_4THWEEK	0.20±0.09	0.20±0.13	0.20±0.11	0.782
LFT_12THWEEK	0.20±0.09	0.24±0.42	0.22±0.30	0.530

Table shows that patients who were selected for Vilazodone were found to have mean baseline serum Direct Bilirubin± S.D. of 0.18±0.06, and it was 0.20±0.13 and 0.24±0.42 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline serum Direct Bilirubin± S.D. of 0.24±0.17, at 4 and at 12 weeks; it was 0.20±0.09 and 0.20±0.09, respectively. It was found that there was no statistically significant change in serum Direct Bilirubin values in both groups.

Table 8: Indirect Bilirubin-A Comparison in two groups studied

Indirect Bilirubin	Treatment Received		Total	P Value
	Group C	Group E		
LFT_BASELINE	1.26±4.43	0.59±0.09	0.94±3.17	0.313
LFT_4THWEEK	1.26±4.63	0.58±0.10	0.93±3.31	0.332
LFT_12THWEEK	1.26±4.83	0.56±0.09	0.92±3.44	0.338

In our study we found that patients who were selected for Vilazodone were found to have mean baseline serum indirect bilirubin ± S.D. of 0.59±0.09, and it was 0.58±0.10 and 0.56±0.09 at 4 and at 12 weeks, respectively. While patients who were selected for Escitalopram were having mean baseline serum ALP of 1.26±4.43 at 4 and at 12 weeks; it was 1.26±4.63 and 1.26±4.83, respectively. It was found that there was no statistically significant change in serum indirect bilirubin values in both group.

Table 9: Haemoglobin-A Comparison in two groups studied

Hb	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	12.46±1.37	12.66±1.09	12.55±1.24	0.447
4th Week	12.31±1.19	12.22±1.09	12.27±1.14	0.684
12th Week	12.44±1.14	12.51±1.17	12.47±1.15	0.751

Table shows that patients who were selected for Vilazodone were found to have mean baseline Haemoglobin ± S.D. of 12.66±1.09, and it was 12.22±1.09 and 12.51±1.17 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline haemoglobin of 12.46±1.37 at 4 and at 12 weeks; it was 12.31±1.19 and12.44±1.14, respectively. It was found that there was no statistically significant change in haemoglobin values in both groups.

Table 10: Lymphocyte-A Comparison in two groups studied

Lymphocyte	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	30.24±8.37	30.59±8.02	30.41±8.16	0.838
4th Week	30.83±9.38	30.82±8.08	30.82±8.72	0.995
12th Week	30.60±9.57	30.80±8.10	30.70±8.83	0.916

In our study we found that patients who were selected for Vilazodone were found to have mean

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lymphocyte ± S.D. of 30.59±8.02, and it was 30.82±8.08 and 30.80±8.10 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline lymphocyte of 30.24±8.37 at 4 and at 12 weeks; it was 30.83±9.38 and 30.60±9.57, respectively. It was found that there was no statistically significant change in serum lymphocyte values in both groups.

Table 11: Monocyte-A Comparison in two groups studied

Monocyte	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	5.68±1.89	6.50±3.04	6.08±2.54	0.120
4th Week	6.07±1.93	6.17±2.31	6.12±2.11	0.811
12th Week	5.59±2.04	5.76±2.52	5.67±2.28	0.723

Table no. show that the patients who were selected for Vilazodone were found to have mean monocyte ± S.D. of 6.70±2.99 and it was 6.17±2.31 and 5.76±2.52 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline monocyte of 5.68±1.89 at 4 and at 12 weeks; it was 6.07±1.93 and 5.59±2.04, respectively. It was found that there was no statistically significant change in serum monocyte values in both groups.

Table 12: Neutrophil-A Comparison in two groups studied

Neutrophil	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	61.69±11.00	64.02±13.82	62.83±12.44	0.373
4th Week	60.83±12.18	64.86±14.26	62.80±13.32	0.152
12th Week	60.80±11.81	63.92±17.64	62.33±14.94	0.326

In our study we found that patients who were selected for Vilazodone were found to have mean neutrophils ± S.D. of 64.02±13.82 and it was 64.86±14.26 and 63.92±17.64 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline of 61.69±11.00 at 4 and at 12 weeks; it was 60.83±12.18 and 60.80±11.81, respectively. It was found that there was no statistically significant change in serum neutrophil values in both groups.

Table 13: Eosinophil-A Comparison in two groups studied

Eosinophil	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	9.21±41.71	2.29±1.06	5.82±29.87	0.269
4th Week	7.68±33.52	2.98±4.09	5.38±24.12	0.358
12th Week	7.43±34.32	2.35±3.02	4.95±24.62	0.331

In our study we found that patients who were selected for Vilazodone were found to have meaneosinophil ± S.D. of 2.29±1.06 and it was 2.98±4.09 and 2.35±3.02 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline of 9.21±41.71 at 4 and at 12 weeks; it was 7.68±33.52 and 7.43±34.32, respectively. It was found that there was no statistically significant change in serum eosinophil values in both groups.

Table 14: Basophil-A Comparison in two groups studied

Basophil	Treatment Received		Total	P Value
	Group C	Group E		
Baseline	0.35±1.31	0.07±0.17	0.21±0.95	0.156
4th WEEK	0.33±1.23	0.02±0.09	0.18±0.89	0.094+
12th Week	0.33±1.30	0.00±0.45	0.17±0.94	0.104

Table show that patients who were selected for Vilazodone were found to have mean basophil ± S.D. of 0.07±0.17, and it was 0.02±0.09 and 0.00±0.45 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline of 0.35±1.31 at 4 and at 12 weeks; it was 0.33±1.23 and 0.33±1.30, respectively. It was found that there was no statistically significant change in serum basophil values in both groups.

Table 15: Platelets-A Comparison in two groups studied

Platelets	Tre tment Received		Total	P Value
	Group C	Group E		

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Baseline	296.34±81.52	276.50±65.40	286.64±74.35	0.202
4th Week	304.36±56.08	289.38±47.59	297.04±52.36	0.176
12th Week	304.65±54.00	297.79±77.14	301.30±66.04	0.625

Table show that the patients who were selected for Vilazodone were found to have mean platelets ± S.D. of 276.50±65.40, and it was 289.38±47.59 and 297.79±77.14 at 4 and at 12 weeks, respectively.
While patients who were selected for Escitalopram were having mean baseline platelets of 296.34±81.52 at 4 and at 12 weeks; it was 304.36±56.08 and 304.65±54.00, respectively. It was found that there was no statistically significant change in serum platelets values in both groups.

Discussion

In our study, we found that approximately 60% patients were females and 40% were males of 30-40 years age group. More than half of them were from urban areas, and remaining were from rural areas. Among enrolled patients more than two third patients were married, belonging to Hindu religion. Most of patients included in study were educated and having secondary and higher secondary level of education.
Among patients enrolled in study maximum numbers of patients were married women (housewives) followed by employed peoples. In a prospective, observational study on 523 patients, Kuga *et al*. 2017 reported that more number of females were receiving treatment with SSRI as compared to males which are in agreement with our results [7].
More than two third patients were not having any kind of addiction. Maximum no. of patients were from socioeconomic class I and having nuclear family type with 3-6 dependent and 1-2 independent members in the family.
All patients enrolled in the study were free from any kind of medical illness and were not having any treatment history for the same, also there was no family history of any psychiatric illness among family members. In our study most of patients (42.4%) had weight range of 50-60 kg.
We found no significant changes in complete blood count (CBC) and other laboratory investigations such as serum creatinine, serum urea and liver function tests value in patients treated with both the antidepressant drugs.
A new antidepressant introduced in the US is Vilazodone, which combines SERT inhibition with a second property: 5HT1A partial agonism. For this reason, Vilazodone is called a SPARI (serotonin partial agonist/reuptake inhibitor).
The combination of serotonin reuptake inhibition with 5HT1Apartial agonism has long been known by clinicians to enhance the antidepressant properties and tolerability of SSRIs/SNRIs in some patients.
5HT1A partial agonist actions plus SERT inhibition can also be attained by augmenting SSRIs/SNRIs with the 5HT1A partial agonist buspirone.
However, this is not identical to the actions of Vilazodone since buspirone and its active metabolite 6-hydroxybuspirone are weaker 5HT1A partial agonists than Vilazodone and are estimated to occupy fewer 5HT1A receptors for a shorter time at clinically administered doses than does Vilazodone [8].
Buspirone and 6-hydroxybuspirone also bind to 5HT1A receptors with lower affinity than5HT itself, whereas Vilazodone binds to 5HT1A receptors with higher affinity than 5HT.
This suggests that administration of buspirone as an augmenting agent to an SSRI/SNRI likely results in 5HT1A receptor occupancy that occurs more robustly in states of low 5HT levels and not as robustly in states of high 5HTlevels, whereas administration of Vilazodone results in binding to 5HT1A receptors even in the presence of 5HT.
Another difference between buspirone plus an SSRI/SNRI versus Vilazodone is that when buspirone augments an SSRI, the buspirone is generally dosed so that about 10-20% of 5HT1A receptors are occupied and the SSRI is dosed so that about 80% of SERTs are blocked.
On the other hand, human neuro imaging studies suggest that Vilazodone is dosed so that about 50% of both SERTs and 5HT1A receptors are occupied. Whether this accounts for clinically significant differences between the administration of Vilazodone monotherapy and the augmentation of SSRIs/SNRIs with buspirone is not known, but it could account for the apparent lesser incidence of sexual dysfunction with Vilazodone than with either SSRIs alone or with the augmentation of SSRIs with buspirone.
It is not known whether the enhanced efficacy of buspirone combined with SSRIs for depression demonstrated in clinical trials for patients who fail SSRI monotherapy also applies to Vilazodone, as appropriate clinical trials to determine this have not yet been conducted [9].
In animal models, adding 5HT1A partial agonism to SSRIs causes more immediate and robust elevations of brain 5HTlevels than SSRIs do alone. This is thought to be due to the fact that 5HT1A partial agonists are a type of “artificial serotonin” selective especially for presynaptic somatodendritic 5HT1A autoreceptors and that 5HT1A partial agonist action occurs immediately after drug is given.
Thus, 5HT1A immediate partial agonist actions are theoretically additive or synergistic with simultaneous SERT inhibition, since this leads to faster and more robust actions at 5HT1 Asomatodendriticautoreceptors than with SERT inhibition alone, including their downregulation.
This hypothetically causes faster and more robust elevation of synaptic5HTN than is possible with SSRIs

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alone. In addition, 5HT1A partial agonism with Vilazodone's SPARI mechanism occurs immediately at postsynaptic 5HT1A receptors, with actions at these receptors that are thus faster and with a different type of stimulation compared to the delayed full agonist actions of serotonin itself when increased by SERT inhibition alone [10].

Conclusion

Our study showed no significant changes in complete blood count (CBC) (table 28-35) and Other laboratory investigations such as serum creatinine, serum urea and liver function tests values (Table no. 21-27) in patients treated with both the antidepressant drugs.

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