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Original Article

Impact of Vortioxetine and Fluoxetine on Cognition and Health Related Quality of Life among Major Depressive Disorder Patients with and without Metabolic Syndrome

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ABSTRACT

Background: Vortioxetine had a positive effect on cognitive function and Health Related Quality of Life (HRQoL), while fluoxetine produced conflicting effects. The effects of study drugs on HRQoL and cognitive function in Metabolic Syndrome (MS) patients are uncertain. This study examines the effect of vortioxetine and fluoxetine in cognition and HRQoL with and without MS. **Materials and Methods:** Open-label, prospective, randomized controlled trial in the psychiatry department, patients were assigned either vortioxetine (group A) or fluoxetine (group B) and observed MS risk using International Diabetes Federation criteria, cognitive risk with the Saint Louis University Mental Status Examination score (SLUMS), and HRQoL using the RAND 36 questionnaire at baseline and at each visit (4,8,12,16,20 and 24 weeks). **Results:** We examined 122 MDD patients, sixty in Group A (26 had MS and 34 were non-MS) and sixty-two in group B (32 had MS and 30 were non-MS). Groups A and B were compared using an independent sample t-test. According to SLUMS score group B exhibited mild cognitive impairment in comparison to group A in both MS and non-MS patients. The RAND 36 questionnaire found better HRQoL in group A than group B for MS, including physical function, role physical, emotional well-being, energy/fatigue, emotion well-being, social function, and general health. In non-MS patients, group A had better physical function and role physical than group B. **Conclusion:** Vortioxetine shows greater potential as a therapeutic alternative for MDD patients with MS and cognitive function and improves HRQoL than fluoxetine.

Keywords: Adverse drug reaction, Antidepressants, Major depressive disorder, Metabolic syndrome.

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INTRODUCTION

Depression is a devastating mental illness characterized by mood disorders, commonly referred to as Major Depressive Disorder (MDD), clinical depression, or melancholia. Depression is prevalent in a significant portion of individuals in human studies.[1] Based on recent World Health Organization (WHO) data; MDD affects approximately 3.8% of the global population, with an estimated 280 million individuals worldwide experiencing this mental health condition.[2]

The Metabolic Syndrome (MS), conceptualized as a cluster of cardiovascular risk factors, obesity, hypertension, hyperglycemia and atherogenic dyslipidemia - which in co-occurrence substantially increase the risk of CVD and type 2 Diabetes Mellitus (DM2), is widely regarded as a useful clinical tool in the prevention of these conditions.[3] Studies have suggested that there is an increased risk of developing Metabolic Syndrome (MS) in depressive patients taking anti-depressants.[4,5] An Evidence based study have concluded that there is an association between the development of MS and Selective Serotonin Reuptake Inhibitors (SSRIs), but it might be dependent upon the choice of diagnostic criteria and SSRI serum concentration or dose.[6]

The risk of developing MS is increased by twice in people who are suffering from MDD, which further underscores the importance

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of finding effective treatment options that address both mental and physical health.[7,8]

Cognitive symptoms are common in MDD and have been shown to be present up to 94% of the time during depressive episodes and up to 44% of the time during periods of remission.[9] Many clinical and epidemiological studies have suggested that MS plays an important role in the progression of cognitive impairment.[10,11] MS is a combination of cardiovascular risk factors (abdominal obesity, dyslipidemia, hyperglycemia, and hypertension).[12] Over the last few years, extensive research and multiple reviews have suggested that there is a link between MS and cognitive impairment.[13] On contradictory to the former statement, few studies have demonstrated that MS can cause cognitive decline.[14,15] The mechanism behind the cognitive decline was considered to be the effects of MS components leading to dementia.[15,16]

Antidepressant drugs constitute the standard of care for MDD, whereby most patients will receive SSRIs as first-line pharmacotherapy.[17] SSRIs were found to have the greatest positive effect on cognition for depressed participants, as compared to the other classes of antidepressants analysed.[18]

Depression has significant effects on quality of life, comparable to chronic medical disorders, adequate treatment is associated with a significant impact on Health Related Quality of Life (HRQOL).[19] A growing number of studies have investigated the association between MS and the HRQOL. Most studies have shown that MS is associated with a lower HRQOL.[20,21] However, the results are diverse. A study from Japan found that a number of MS components was negatively associated with general health but positively associated with mental health.[22] A study in Korea did not find a significant association between MS and the HRQOL after adjusting for confounding factors.[23] Furthermore, sex and body mass index (BMI) may affect the relationship between MS and the HRQOL. Some studies have observed the detrimental effects of MS on the HRQOL only in women.[24] Another study in Korea showed that individuals with MS suffered from a stronger impairment in obesity-specific quality of life.[25]

Although, studies with fluoxetine effect on cognitive function and HRQOL does provide mixed conclusion,[26,27] on the flip-side studies with vortioxetine had reported improvement in cognitive function and HRQoL in MDD patients.[28-30] However, the effectiveness of study drugs and their influence on quality of life and cognitive effect with long term treatment in patients with the risk of metabolic disorder remain uncertain. Therefore, this study aims to investigate the fluoxetine and vortioxetine on cognition and HRQoL with the risk of MS in MDD.

MATERIALS AND METHODS

Study design

A prospective, open-label, Randomized Controlled Trial (RCT) was carried out in the psychiatry department at the Sri Ramachandra Hospital, Chennai. The participants were allocated into two groups using a computer-generated list of random numbers under the supervision of a medical practitioner in the psychiatry department, either with Fluoxetine 20 mg or Vortioxetine 10 mg, and the baseline data were recorded and followed up for 24 weeks. The study was carried out from February 2022 to January 2023 over a 12-month period.

Ethical consideration

Participation was voluntary, with patients and caregivers being duly informed about the research objectives. The study protocol received approval from the institutional ethics committee (IEC/20/SEP/158/33). Our study is prospectively registered with the Clinical Trial Registry, India (CTRI/2021/07/034892). Participants in the study provided written informed consent, and the investigation was carried out in accordance with the Indian Council of Medical Research's (ICMR) revised "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants" in 2017.

Sample size

The sample size was determined using n Master software version 29.0, with a power of 0.80, an alpha error of 0.05, and an effect size of 0.4656, with the Standard Deviation (SD) of group A being 7.0 and group B being 8.0 with a 95% Confidence Interval (CI). The required sample size per group is 60. By including the attrition rate of 15%, about 69 samples were recruited in each group of the study.

Study participants

Individuals between the ages of 18 and 60, of both genders, with a diagnosis of mild to moderate MDD based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), patients with Hamilton Depression Scale (HAM-D) scores between ≥7 and ≤24, and treated with either Vortioxetine (10 mg/day) or Fluoxetine (20 mg/day) and if they provided both verbal and written informed consent to participate in the study, were included. Those who had a concomitant psychological illness or any psychoactive medications and having metabolic abnormalities followed International Diabetes Federation (IDF) criteria such as Triglycerides (TGs) levels above ≥150 mg/dL, High Density Lipoprotein (HDL)<40 mg/dL in males, <50 mg/dL in females, Fasting Plasma Glucose (FPG) 100 mg/dL, Blood Pressure (BP) ≥130/85 mm Hg and waist circumference ≥90 cm for men, ≥80 cm for women (south Asian ethnic group), Known cases of Type 2 diabetes, obesity, valvular disease, sleep disorder, Polycystic Ovarian Disease (PCOD), substance abuse, alcohol abuse, eating disorders, individuals on a diet, any known allergies with study drugs, and pregnant and lactating women were excluded from this study. Furthermore, those who were diagnosed with cognitive impairment based on scores from the Saint Louis University Mental Status (SLUMS) questionnaire, those who were

unable to provide past medication history, those with suicidal thoughts, were excluded.

Clinical outcome measures

The participants in this study completed a standardized data collection form to gather information on demographic characteristics (such as gender, age, education level, occupation, and marital status) and clinical data regarding study drugs, personal habits, diabetes-related complications, and concurrent medical comorbidities. MDD was assessed using the HAM-D questionnaire. We obtained various anthropometric factors, such as weight, waist size, SBP, and DBP. Besides, 10 mL of whole blood will be collected from the patients by the phlebotomist to evaluate the subsequent biochemical aspects: FPG, HDL, and TGs. Clinical and biochemical assessments were conducted at two time points: before starting antidepressant therapy and then at four-week intervals until week 24.

Health Related Quality of Life (HRQoL)

The HRQoL of patients were assessed using RAND-36 questionnaire, which contains 36-items measuring health across eight areas or domains: Physical Functioning (10 items); Social Functioning (2 items); Role Limitations due to physical problems (RP, 4 items); Role Limitations due to emotional problems (3 items); Emotional well-being (5 items); Energy/ fatigue (4 items); Bodily Pain (2 items), General Health and Health change (6 items). For each dimension, scores are coded, summed and transformed to generate a score from 0 (worst possible health state) to 100 (best possible health state).[31]

Screening for cognitive impairment

The SLUMS test was chosen for our investigation due to several factors. The SLUMS test demonstrated a high level of accuracy, ranging from 98% to 100%, in detecting dementia.[32] The SLUMS test demonstrated superior ability in detecting mild Cognitive Impairment (CI) compared to other cognitive questionnaires. The SLUMS test demonstrated a sensitivity of 93% for individuals with an education level below high school. The SLUMS evaluation demonstrated a sensitivity of 94% among high school graduates.[32,33] The SLUMS test can be completed in 7 min and is readily accessible for free download online.[34]

Study procedure

Patients who agreed to provide informed consent and also met the inclusion criteria were assessed by the psychiatrist, and then the study participants were randomly assigned to receive either group A as vortioxetine (10 mg/day) or group B as fluoxetine (20 mg/day). They were instructed to report any changes in their dietary habits or appetite and were monitored for 24 weeks. The baseline data of HAM-D score for MDD, waist circumference, FPG, BP, HDL, and TGs for MS, HRQoL using RAND questionnaire and Cognitive impairment using SLUMS were measured before the start of study drugs as well as followed from weeks 4, 8, 12, 16, 20, and 24 with either group A or group B. Patients with elevated waist circumference plus any two of the following four abnormal metabolic parameters such as FPG, TGs, BP (SBP and DBP) and HDL were been classified as MS group and others as Non MS group. The reference ranges for MS were followed according to IDF criteria.

Statistical analysis

The data were meticulously analyzed using IBM SPSS Statistics for Windows, version 29.0. Armonk, New York: IBM Corporation. Descriptive statistics were employed to analyze the findings, applying frequency and percentage analysis for categorical variables and mean and standard deviation for continuous variables. To find the significant difference between the bivariate samples for independent groups the independent sample t-test was used. The study applied repeated measures ANOVA with Bonferroni correction to control the type I error across multiple comparisons. The Chi-Square test assessed the statistical significance of categorical data. All statistical tests were two-tailed, with a significance level of $p<0.05$.

RESULTS

A total of 218 patients underwent a thorough screening process for this study, and 74 participants were excluded from the study due to failure to meet inclusion criteria (n=48), withdrawal of consent (n=12), and lack of willingness to participate in randomization (n=7). The remaining 144 patients were randomly allocated to one of two treatment groups. Twenty-two participants dropped out of the study due to a variety of reasons, such as withdrawal of consent within the first week, discontinued intervention, travel-related issues, and relocation to another state. In total, we examined 122 patients diagnosed with MDD, divided into two groups: 60 patients in group A and 62 patients in group B (Figure 1). Table 1 exhibits the demographic and clinical characteristics of the study participants.

Among sixty patients in Group A, 26 had MS and 34 were non-MS patients. Similarly, in Group B, with sixty-two patients, 32 had MS and 30 were non-MS patients. This study found a statistically insignificant difference (p=0.337) in overall remission of depression between the two groups over a 24-week treatment period. The remission rates observed in this study were 74.21% for Vortioxetine (n=60) and 75.50% for Fluoxetine (n=62) following a 24-week treatment period. Throughout the study, there were no discernible changes in the patient's appetite or food intake. This conclusion was reached after examining the patient's responses to a standardized questionnaire that examined their intake of carbohydrates, lipids, and proteins as well as their appetite at each visit.

Effect of study drugs on cognition between MS and non-MS patients

Adult cognitive capacity may be assessed with the SLUMS, a screening instrument consisting of eleven items. There are a total of thirty-three questions in the SLUMS test, with three pertaining to orientation, nine to reasoning, and six to memory.[35] Table 2 presents a comparison of the SLUMS scores between the MS and non-MS groups. The cognitive impact of patients among two groups in MS and non-MS was assessed using the SLUMS questionnaire, and the p value was compared between groups using an independent sample t-test and within groups using a repeated measure ANOVA. Out of the 26 patients in the MS group, 4 (15.4%) in group A and 12 (37.5%) in group B had SLUMS scores below 26, indicating mild cognitive impairment. In the non-MS group, 2 (5.9%) in group A and 9 (30%) in group B also had SLUMS scores below 26, indicating mild cognitive impairment. A significant mean association was found at week 24 (p=0.005) between group A and group B in the MS group. In the non-MS group, a statistical correlation was observed from week 20 onward (p=0.001), suggesting that group B exhibited mild cognitive impairment in comparison to group A. Similarly, in the non-MS group, a significant mean association was observed at week 16 (p=0.005), implying that group B showed mild cognitive impairment compared to group A. Within-group comparison also revealed a significant mean association at week 24 (p=0.005) with mild impairment in group B compared to group A in both MS and non-MS patients.

Effect of study drugs on HRQoL between groups between MS and Non MS patients

Table 3 compares the RAND-36 domain scores for the MS and non-MS groups. The HRQoL of patients among two groups

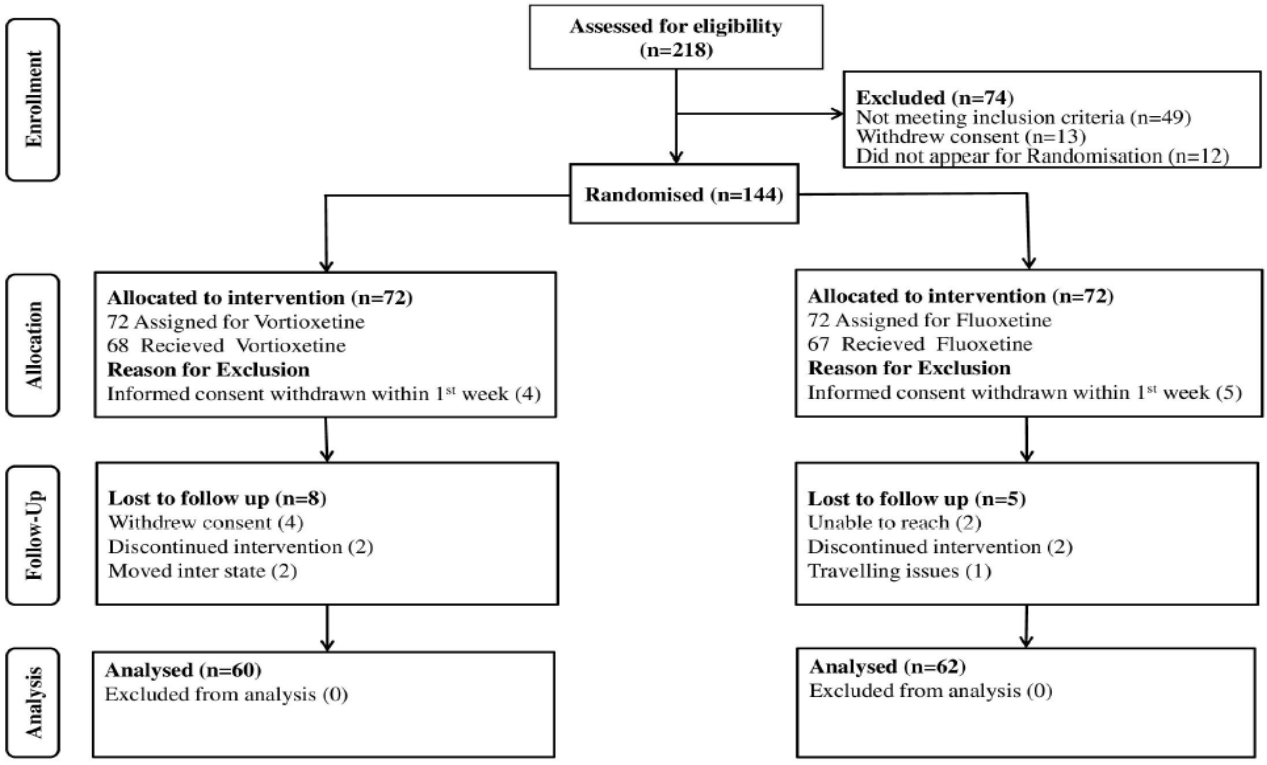

Figure 1: CONSORT flow diagram.

Table 1: Baseline characteristics of the study population.

Characteristics	Group A *n*=60 (%)	Group B *n*=62 (%)	*p* value
Age in years	36.98±6.9	38.86±8.6	0.112
Gender			
Male	29 (48.3)	32 (51.61)	0.621
Female	31 (51.7)	30 (48.39)	
Occupation			

Characteristics	Group A *n*=60 (%)	Group B *n*=62 (%)	*p* value
Employed	28 (46.7)	27 (43.5)	0.454
Unemployed	11 (18.3)	15 (24.2)	
Business	09 (15.0)	05 (8.1)	
Daily wages	10 (16.7)	12 (19.4)	
Pensioner	02 (3.3)	03 (4.8)	
Education			
Middle school/ Illiterate	22 (36.7)	29 (46.8)	0.568
High school/Graduate	38 (63.3)	33 (53.2)	
Marital status			
Single	28 (46.7)	27 (43.5)	0.454
Married	11 (18.3)	15 (24.2)	
Separated	09 (15.0)	05 (8.1)	
Divorced	10 (16.7)	12 (19.4)	
Widowed	02 (3.3)	03 (4.8)	
Family type			
Nuclear	24 (40.0)	25 (40.3)	0.142
Joint	25 (41.7)	24 (38.7)	
Living alone	11 (18.3)	13 (21.0)	
Socioeconomic class			
Upper	07 (11.7)	04 (6.5)	0.381
Upper middle	12 (20.0)	08 (12.9)	
Lower middle	29 (48.3)	27 (43.5)	
Upper lower	08 (13.3)	16 (25.8)	
Lower	04 (6.7)	07 (11.3)	
Duration of current depression (months)	2.3 (1.0)	2.4 (1.1)	0.115
HAM-D score	18.4±3.6	17.9±3.6	0.213
WC (cm)	83.06±5.6	81.27±7.1	0.322
FPG (mg/dL)	93.3±6.9	94.9±6.1	0.322
TGs (mg/dL)	137.8±6.9	137.2±7.6	0.517
HDL (mg/dL)	53.1±8.1	53.7±7.2	0.662
Blood Pressure			
SBP (mm Hg)	125.1±4.2	124.6±5.4	0.785
DBP (mm Hg)	83.1±2.1	82.4±2.8	0.124
SLUMS score	27.3±1.3	27.2±0.8	0.228
MS	26 (43.4%)	32 (51.61%)	0.114
Non- MS	34 (56.6%)	30 (48.49%)	0.121

Continuous variables were expressed as the mean±standard deviation, categorical values were presented as n (%); Group A: vortioxetine 10 mg, Group B: fluoxetine 20 mg; **MS:** Metabolic syndrome; **non-MS:** Non metabolic syndrome; **HAM-D:** Hamilton depression rating scale; **FPG:** Fasting plasma glucose; **TGs:** Triglycerides; **HDL:** High density lipoprotein; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **SLUMS:** Saint Louis University Mental Status score; **MS:** Metabolic syndrome; **Non-MS:** Non metabolic syndrome; *p* value significant at <0.05.

(MS and non-MS) was assessed using a licensed RAND 36 questionnaire and compared using an independent sample t-test. All eight characteristics of the RAND 36 scales were observed from baseline to 24 weeks. Among the MS group, the various RAND 36 domains such as physical function (p=0.005), role physical (p=0.030), emotional (p=0.001), energy/fatigue (p=0.005),

emotional well-being (p=0.001), social function (p=0.041), and general health (0.002) have been found to be improved except bodily pain (p=0.144) in group A compared to group B. Similarly, we compared the two groups among non-MS patients using the RAND-36 domain score and found significant improvement only in physical function (p=0.005) and role physical (p=0.011) in group A compared to group B.

DISCUSSION

Cognitive disorders are a prominent characteristic of depression. A recent meta-analysis study discovered a significant association between depression and a twofold higher risk of developing dementia.[36] Clinical and epidemiological research has shown that MS is a factor in the development of cognitive impairment.[37,10] The aging study reported that MS is linked to cognitive decline. The study found that the composite measure of MS is more strongly

Table 2: Within and between-group comparison of SLUMS scores on MS and non-MS groups in MDD patients.

Treatment period (Weeks)	MS-SLUMS score (n=58)		p value (Between group)	non-MS-SLUMS score (n=64)		p value (Between group)
	Group A n=26	Group B n=32		Group A n=34	Group B n=30	
0	27.2±0.8	27.3±1.3	0.244	28.0±2.2	27.8±1.4	0.425
4	27.5±0.9	27.4±1.1	0.432	27.9±2.1	27.7±3.3	0.384
8	27.3±1.8	27.0±1.3	0.321	27.8±2.3	27.5±4.2	0.300
12	27.1±1.5	26.3±1.3	0.334	27.4±2.8	27.2±3.1	0.112
16	27.0±1.6	26.5±1.4	0.462	27.8±3.5	26.8±4.2	0.005
20	26.9±1.9	26.2±2.0	0.211	27.9±3.1	26.6±3.1	0.001
24	27.1±1.0*	26.0±1.5*	0.001	28.2± 2.5*	26.2± 3.7*	0.001

Values are presented as mean±standard deviation; group A: vortioxetine 10 mg; group B: fluoxetine 20 mg; **MDD:** Major depressive disorder; **MS:** Metabolic syndrome; **non-MS:** Non-Metabolic syndrome; **SLUMS:** Saint Louis University Mental Status score; p value for between group comparison using independent sample t-test; p value for within group comparison using repeated measures ANOVA; *indicates within group analysis ($^{*}p$<0.05, $^{**}p$<0.01, $^{***}p$<0.001); p value significant at <0.05.

Table 3: Between-group comparison of RAND-36 score on MS and non-MS group in MDD patients.

RAND-36 domain	Treatment period (Weeks)	MS-RAND 36 score (n=58)		p value	non-MS-RAND 36 score (n=64)		p value
		Group A (n=26)	Group B (n=32)		Group A (n=34)	Group B (n=30)	
Physical function	0	45.29±9.80	43.20±7.30	0.125	49.37±4.80	48.37±4.80	0.223
	24	62.00±6.43	58.57±6.45	0.005	68.21±2.85	55.27±1.10	0.005
Role physical	0	49.02±4.92	47.96±4.92	0.150	47.95±7.01	48.21±6.21	0.214
	24	65.31±2.85	58.44±2.92	0.030	66.01±9.00	59.35±8.54	0.022
Role emotional	0	48.18±5.35	47.78±3.20	0.244	44.21±6.87	44.44±7.14	0.187
	24	76.26±4.36	68.24±4.49	0.001	78.22±8.55	74.00±8.26	0.266
Energy/ fatigue	0	53.98±5.52	52.98±5.52	0.321	58.25±8.74	57.54±8.20	0.443
	24	69.89±3.55	62.69±3.48	0.005	73.74±7.04	70.68±4.28	0.350
Emotion wellbeing	0	59.61±5.56	58.61±5.56	0.401	53.36±7.41	54.00±8.88	0.222
	24	77.22±3.31	69.62±3.40	0.001	79.36±8.51	72.94±9.34	0.304
Social Function	0	48.98±7.46	47.85±7.46	0.688	49.47±8.47	48.57±9.34	0.457
	24	74.49±4.49	69.24±4.63	0.041	65.36±5.74	63.02±7.62	0.201
Bodily Pain	0	57.61±5.81	58.61±5.81	0.122	59.51±6.22	59.31±4.28	0.230
	24	69.87±4.49	66.25±4.56	0.144	69.25±8.47	65.87±7.22	0.241
General Health	0	69.58±4.10	68.58±4.10	0.712	66.35±7.11	67.58±5.23	0.640
	24	80.11±4.05	78.65±4.07	0.002	83.32±5.55	81.00±7.00	0.121

Values are presented as mean±standard deviation; group A: vortioxetine 10 mg; group **MS:** Metabolic syndrome; **non-MS:** Non-Metabolic syndrome; group A: vortioxetine 10 mg; group B: fluoxetine 20 mg; RAND 36; health related quality of life score; Independent sample t-test; p value significant at <0.05.

associated with higher odds of cognitive decline compared to its individual components.[38]

The current investigation observed that Vortioxetine exhibited superior cognitive enhancement in the non-MS group relative to the MS group, as compared to Fluoxetine. In contrast, few studies have found no link between MS and cognitive impairment.[40,39] Additionally, Liu CL *et al.* have reported that MS in later life has a positive impact on cognitive function.[41] Consistent with our research, numerous studies have found a positive correlation between MS and a higher likelihood of cognitive impairment than non-MS group.[33,42,43]

A meta-analysis was conducted to examine the effects of various classes of antidepressants, such as SSRIs and SNRIs, on cognitive deficits associated with MDD, and these findings suggest that conventional antidepressants may have some positive impact on cognitive deficits in MDD. However, it is important to note that most of the studies supporting this conclusion have limited sample sizes.[44,45] and a study from Bennabi D *et al.* demonstrated that vortioxetine distinguishes itself from other antidepressants in terms of effects on cognitive function.[46]

This current study found that fluoxetine treatment resulted in mild cognitive impairment in the MS group which was not found in the non-MS group. Few researchers have reported a detrimental effect on cognitive function resulting from fluoxetine, which was anticipated due to the short-term use of antidepressants.[47,48] In contrast to our own findings, prior research has indicated that fluoxetine may potentially augment cognitive function among individuals diagnosed with depression.[49]

Several studies have investigated the impact of depression and MS on HRQoL, finding a decline in QoL.[50-52] In the present study we observed HRQoL decline more in MS group compared to non-MS group. This study have examined the impact of vortioxetine and fluoxetine on Health-Related Quality of Life (HRQoL) using the RAND 36 questionnaire in individuals with and without MS and observed that vortioxetine was superior to fluoxetine in enhancing physical function, emotional well-being, energy/fatigue, social function, and general health among individuals with MS. However, there was no significant difference between the two groups in terms of bodily pain. Similarly, in the non-MS group, a significant difference was observed only in the physical domains, and the vortioxetine group exhibited superior improvement in overall HRQoL than the fluoxetine group. A meta-analysis in adults found that vortioxetine treatment resulted in statistically significant improvements in vitality, social functioning, role emotional, and mental health scores within the SF-36 domain, compared to placebo and other antidepressants.[30,53] In contrast, few studies have reported that MDD patients who were on fluoxetine were found to have better HRQoL than with other antidepressants.[30,54] and a study from vetter *et al.* observed that MS sin itself is not associated with a decreased HRQoL, but other factors such as obesity, depression, and greater disease burden may have significant effects on quality of life in this population.[55]

Strength

This research is the first to investigate the study drug effect on cognition and HRQoL among MS and non-MS groups in MDD patients, and this study may provide valuable insights into the well-being of patients and inform treatment strategies that address cognitive impairment, HRQoL, and metabolic dysregulation observed with study drugs. Moreover, increased follow-up visits allow researchers to gather more data on the study drug's long-term effects on cognitive function, HRQoL, and metabolic parameters. This, in turn, enhances the comprehension and treatment of MDD.

Limitations

Despite the promising effects of vortioxetine and fluoxetine on cognition and HRQoL among MS and non-MS patients, there are a few limitations that require attention. Cognitive impairment was assessed solely using the SLUMS questionnaire, which is not considered a comprehensive neurocognitive assessment. Additionally, the study had a smaller sample size and employed an open-label trial design.

CONCLUSION

This study examines the efficacy of vortioxetine and fluoxetine in the treatment of MDD patients, with and without MS. Our findings reveal that vortioxetine not only displays a lower incidence of MS compared to fluoxetine but also exhibits improvements in cognitive function and HRQoL for both MS and non-MS patients. These results suggest that vortioxetine may be a promising therapeutic option for MDD patients with MS and cognitive dysfunction and can significantly enhance the HRQoL of MS patients when compared to fluoxetine treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflicts of interest.

ABBREVIATIONS

BMI: Body Mass Index; **MDD:** Major Depressive Disorder; **SSRIs:** Selective Serotonin Reuptake Inhibitors; **MS:** Metabolic Syndrome; **DSM-V:** Diagnostic and Statistical Manual of Mental Disorders V; **HAM-D:** Hamilton Depression Scale; **TGs:** Triglycerides; **HDL:** High Density Lipoprotein; **FPG:** Fasting

Plasma Glucose; **BP:** Blood Pressure; **HRQoL:** Health Related Quality of Life; **SLUMS:** Saint Louis University Mental Status.

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