ORIGINAL RESEARCH

A Feasibility Study of Patients with Major Depression and Substance Use Disorders: Vortioxetine as Maintenance Treatment

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Background: Limited studies have evaluated the effectiveness of vortioxetine in real-world settings, and none of them has involved patients with dual depression (major depressive disorder [MDD] and substance use disorder [SUD]). The objective of the study was to describe the effectiveness of vortioxetine in clinical practice and determine its effect on affective symptoms, cognitive function, quality of life, and substance use in patients with MDD and SUD.

Methods: Post-authorization, retrospective, multicenter, descriptive, and observational study in 80 patients with MDD and SUD receiving a maintenance treatment with vortioxetine for six months between January 2017 and April 2021.

Results: Compared with baseline, scores significantly decreased after 3 and 6 months of treatment in the Montgomery-Åsberg Depression Rating Scale total (from 28.9 to 17.7 and 12.0), and global functional impairment of the Sheehan Disability Inventory (from 26.3 to 19.1 and 16.7). The number of correct answers in the symbol digit modalities test significantly improved during vortioxetine treatment (from 40.4 to 43.8 and 48.4). Regarding the clinical global impression scale, the score for disease severity significantly decreased from 3.8 to 3.0 and 2.4. Compared with baseline, there was a significant reduction in consumption of practically all substances, especially of alcohol, cannabis, and cocaine.

Conclusion: Vortioxetine was effective in clinical practice for alleviating depressive symptoms and functional impairment, and in improving cognitive and executive functions and disease severity in patients with MDD and SUD. Moreover, the treatment with vortioxetine favored a reduction in substance use and the severity of the SUDs.

Keywords: vortioxetine, major depressive disorder, substance use disorder, dual disorder, major dual depressive disorder, real-world evidence

Introduction

Major depressive disorder (MDD) is a common illness and one of the leading causes of burden of disease and disability-adjusted life years worldwide due to its devastating impact on individuals, families, and society.[1] According to the World Health Organization (WHO), depression affects more than 264 million people worldwide.[2] From a clinical neuroscience and transdiagnostic perspective (beyond DSM-5), depression is considered a brain disorder affecting emotional regulation which is also involved in symptoms of substance use, eating, anxiety, and borderline personality disorders.[3] Depressed patients present concurrent addictive disorders, such as substance use disorders (SUD) or behavioral addictions (like gambling

disorder);[4] leading to a clinical condition called as dual depression, consisting of depression with concurrent SUD.[5] Indeed, approximately one third of patients with MDD have a SUD.[6] A systematic review and meta-analysis with data from epidemiological surveys between 1990 and 2014 revealed significant associations between MDD and SUDs, especially with illicit drugs and alcohol.[7] Patients with dual depression show unique clinical characteristics, including more cognitive symptoms, a lower treatment adherence, a higher number of suicide attempts[6,8] than those with no dual disorders, in addition to being more refractory to conventional therapies. Given the phenotypic heterogeneity in MDD, supported by several genetic and neurobiological studies that state that these conditions are not discrete categories but part of a continuum or affective disorder spectrum, the treatment approach based on a single therapy is changing toward a personalized treatment.[5,9] From a neuroscience perspective, it currently seems clear that there are many phenotypes of depression and many antidepressants with different mechanisms of action. When treating a patient with dual depression, knowing whether all antidepressants are equally effective is imperative. Dual depression seems to be a different phenotype needing a new approach. Antidepressant drugs, mainly selective serotonin (5-HT) reuptake inhibitors (SSRIs), are the primary psychopharmacological treatment for patients with MDD. However, several systematic reviews and meta-analyses have demonstrated that SSRIs, with a unimodal mechanism of action, are not effective for these patients.[10,11] Limited response to the standard treatment for dual depression increases suffering and risk of suicide.

Thus, new psychopharmacological treatments are needed to treat dual depression.[12] In this sense, the emergence of drugs with a multimodal mechanism of action should be considered as a therapeutic option.[13] Vortioxetine is a multimodal antidepressant drug that received approval in 2013 for the treatment of MDD by both the US Food and Drug Administration and European Medicines Agency.[14] In vitro studies have revealed that vortioxetine functions as a 5-HT_{1A} receptor agonist, a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, and an inhibitor of the serotonin transporter.[15,16] Various short- and long-term randomized clinical trials have also evidenced the superior therapeutic benefit of vortioxetine over placebo in the treatment of depressive and cognitive symptoms in MDD patients. Moreover, vortioxetine has demonstrated efficacy in patients with inadequate response to SSRIs or serotonin-noradrenaline reuptake inhibitors (SNRI).[17] To our knowledge, limited studies have evaluated the effectiveness of vortioxetine in real-world settings,[18–20] and only one has involved patients with MDD and substance use disorder (SUD).[21] Therefore, the objective of the present study was to describe the effectiveness of vortioxetine in routine clinical practice and determine its effect on affective symptoms, cognitive function, quality of life, and substance use in patients with MDD and SUDs.

Materials and Methods
Study Design
This post-authorization, retrospective, multicenter, descriptive, and observational study included consecutive patients with MDD and SUD receiving a maintenance treatment with vortioxetine for six months between January 2017 and April 2021. The maintenance protocol consisted of a program in which patients were evaluated on a rolling basis and based on a series of objective validated tests, all of which were part of the present study. In the day the patient was included in the study, a cross-evaluation was performed. Patients from a total of six Spanish healthcare centers were included in this study: Hospital General Universitario Gregorio Marañón, Hospital Universitario Vall d'Hebron, Hospital Universitario Dr. Peset de Valencia, CAD Instituto de Adicciones de Madrid, Institute of Neuropsychiatry & Addictions-Parc de Salut Mar de Barcelona and Complejo Asistencial Universitario de Salamanca. Although some of them are general hospitals, all patients were treated in tertiary specialist centres. Inclusion criteria were: males and females aged between 18 and 65 years; with a diagnosis of MDD, according to DMS-5 criteria;[22] receiving maintenance treatment with vortioxetine in the previous six months; and patients with SUD who had complied with the clinical practice protocol for patients with MDD within six months before study inclusion. Pregnant or lactating women and patients with concomitant diseases that may interfere with the evaluation of the analyzed parameters were excluded. A total of six Spanish sites participated in the study. All procedures were in accordance with routine clinical practice and all participants provided informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Gregorio Marañon University Hospital (Madrid, Spain).

Endpoints and Variables

The primary endpoint was the description of vortioxetine effectiveness at three time points (baseline and three and six months after starting vortioxetine treatment) using the Spanish version of the Montgomery-Åsberg Depression Rating Scale (MADRS), the Sheehan Disability Inventory (SDI), the symbol digit modalities test (SDMT), and the clinical global impression (CGI) scale. The MADRS is a 10-item scale used to assess symptom severity in MDD.[23] Each item is rated on a Likert scale that ranges from 0 (absence of depression) to 6 (maximum depression score).[24] This scale establishes the following cut-off points in a 0–60 range: absence of depression (0–6), mild depression (7–19), moderate depression (20–34) and severe depression (35–60). The SDI is a 5-item scale for assessing functional impairment in three domains, including work/school, social life, and family life, perceived stress, and social support.[25] Except for social support, items are scored on a 10-point visual analogue scale arranged in the absence (0), mild (1–3), moderate (4–6), marked (7–9) and extreme (10) impairment subgroups. Social support item is represented as a percentage. The SDMT is an instrument to measure information processing speed, and to detect cognitive impairment.[26] A row of nine boxes filled with different symbols was presented to the participants. Above the row, a symbol digit key, pairing the nine symbols with a number from 1 to 9, is shown. A total of 110 items were presented. By using the symbol digit key, participants were asked to match each symbol in the bottom row with a number as quick as possible. An initial practical task of ten items was performed. The obtained score, with a maximum of 110 points, corresponds to the total number of substitutions in a 90-second interval.[27] The CGI scale is used to evaluate disease pattern severity, which is composed of two subscales: severity of disease, and global improvement.[28] Higher scores are indicative of a higher disease severity. Secondary endpoints included the description of the sociodemographic and clinical characteristics of patients with MDD and SUD, and the changes in SUDs during vortioxetine treatment. To diagnose SUD, for each patient both past and actual history of consumption, the consumption starting age, last consumption, and an estimation of severity, if needed, were evaluated for substances such as alcohol, caffeine-related products, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, tobacco and other substances. Changes in the severity of SUDs were assessed using the Spanish version of the 5-item severity of dependence scale, where each item is rated on a 0–4 Likert scale.[29] Higher scores are representative of greater severities. Relapsing patients were diagnosed according to the DSM-5 criteria.

Statistical Analysis

Continuous variables are expressed as mean, standard deviation (SD), 95% confidence interval (CI95%), or range (minimum and maximum values); whereas categorical ones were represented as absolute and relative frequencies. Comparisons of variables between time points (3- and 6-month of vortioxetine treatment) versus baseline were carried out using the *t*-test or Wilcoxon test, when appropriate. Statistical significance was established at p≤0.05. All statistical procedures were performed using SAS v14.0. Accepting an alpha risk of 0.05 and a bilateral contrast of 90%, 78 subjects were needed to detect a difference equal or higher than 10 units. A standard deviation and withdrawn rate of 25[30] and 15% were assumed respectively.

Results

Study Population

A total of 80 patients were consecutively recruited for the study. None of them was excluded from analyses. Sociodemographic and clinical characteristics of patients are shown in Table 1. They were predominantly males (63.8%, n=51), with a mean age of 45.1 years (SD: 13.8). Most of them had never been married (36.3%, n=29), had primary education (40.0%, n=32), and were unemployed (40.1%, n=32). Half of the sample (51.3%, n=41) had at least one medical comorbidity, most commonly hypertension (16.3% of patients, n=13), obesity (10.0%, n=8), or human immunodeficiency virus infection (8.8%, n=7). The majority of patients experienced recurrent episodes of MDD (81.3%, n=65), mainly of moderate severity. The SUDs were mainly due to alcohol and tobacco use (66.3% [n=53] and 40.0% [n=32] of patients, respectively). The mean dose of vortioxetine was 13.8 mg/day (range: 5–20). At baseline, most of the patients (91.3%, n=73) were receiving another psychopharmacological treatment, mainly antipsychotics (37.5%, n=30), benzodiazepines (36.3%, n=29), anticonvulsants (36.3%, n=29), or other antidepressants (31.3%, n=25; Table 2). In

Table 1 Sociodemographic and Clinical Characteristics of Patients

	Patients (N=80)
Gender, n (%)	
Female	29 (36.3)
Male	51 (63.8)
Age, mean years (SD)	45.1 (13.8)
Marital Status, n (%)	
Never been married	29 (36.3)
Married	16 (20.0)
Separated	19 (23.8)
Divorced	8 (10.0)
Widow	4 (5.0)
Living in partner	4 (5.0)
Dominant hand, n (%)	
Right-handed	70 (87.5)
Left-handed	10 (12.5)
Educational level, n (%)	
No studies	1 (1.3)
Primary education	32 (40.0)
Secondary education	21 (26.3)
University studies	22 (27.5)
Other	4 (5.0)
Employment status, n (%)	
Employed	12 (15.0)
Self-employed	4 (5.0)
Student	8 (10.0)
Responsible for household chores	4 (5.0)
Retired	10 (12.5)
Unemployed (by health reasons)	5 (6.3)
Unemployed (by other reasons)	27 (33.8)
Other	2 (2.5)
Work incapacity	8 (10.0)

(*Continued*)

Table 1 (Continued).

	Patients (N=80)
Comorbidities, n (%)	41 (51.3)
Arterial hypertension	13 (16.3)
Obesity (BMI >30 Kg/m^2)	8 (10.0)
Human immunodeficiency virus	7 (8.8)
Type 2 diabetes mellitus/dyslipidemia	5 (6.3)
Hepatitis (HBV/HCV)	5 (6.3)
Tuberculosis	2 (2.5)
Others	18 (22.5)
Diagnosis of major depressive disorder, n (%)	
One episode	15 (18.7)
Mild	2 (13.3)
Moderate	6 (40.0)
Severe	4 (26.7)
With psychotic features	3 (20.0)
Recurrent episodes	65 (81.3)
Mild	10 (15.4)
Moderate	38 (58.5)
Severe	15 (23.1)
With psychotic features	1 (1.5)
Partial remission	1 (1.5)
Substance use history, n (%)	
Tobacco	32 (40.0)
Alcohol	53 (66.3)
Cannabis	21 (26.3)
Hallucinogens	0 (0.0)
Inhalants	0 (0.0)
Opiates	
Heroin	8 (10.0)
Methadone	1 (1.3)
Others	4 (5.0)

(*Continued*)

Table 1 (Continued).

	Patients (N=80)
Sedatives	8 (10.0)
Stimulants	
Amphetamines	1 (1.3)
Cocaine	25 (31.3)
Others	3 (3.8)
Other substances	3 (3.8)
Pathological gambling	7 (8.8)

Abbreviations: SD, standard deviation; BMI, body mass index; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HBV, hepatitis C virus.

addition, 77.5% of patients (n=62) were receiving non-pharmacological therapy, especially individual psychotherapy (58.1%, n=36). Psychopharmacological and non-pharmacological treatments remained constant at the third and sixth month of follow-up. A total of four patients at baseline (5.0%), one patient after three months (1.3%), and three patients after six months of vortioxetine treatment (3.8%) required inpatient admissions (by symptomatic decompensation, either affective or relapse of the SUD).

In addition, this improvement in the different scales was not dependent of the number of SUD associated to each patient, with no significant differences between patients with a single and several SUDs were observed at every time point (Supplementary Table 1). Finally, the improvement in the scores reported for every scale was also independent of the administered initial vortioxetine dose, since no differences were observed between the different doses at both three and six months. The only exception was observed in the SDMT scale for the 15 mg vortioxetine dose at six months, probably due to the lack of a higher available n (Supplementary Table 2).

Effect of the Vortioxetine Treatment

Total score in MADRS significantly decreased from baseline (mean: 28.9; 95% CI: 26.1–31.7) to the 3-month (mean: 17.7; 95% CI: 15.7–19.7; p<0.001), and the 6-month assessments (mean: 12.0; 95% CI: 10.2–13.9; p<0.001; Figure 1). Similarly, scores from all dimensions of MADRS significantly reduced after 3 and 6 months, compared with baseline (Supplementary Table 3). The score from the global functional impairment of the SDI scale also significantly declined between baseline (mean: 26.3; 95% CI: 24.2–28.5), 3-month (mean: 19.1; 95% CI: 17.0–21.1; p<0.001), and 6-month treatment (mean: 16.7; 95% CI: 14.6–18.7; p<0.001). Scores of all domains of SDI scale were significantly lower at the 3- and 6-month treatment than baseline. The number of correct answers in the SDMT significantly improved from baseline (mean: 40.4; 95% CI: 37.8–42.9) to the third (mean: 43.8; 95% CI: 41.5–46.1; p<0.001), and sixth months (mean: 48.4; 95% CI: 45.6–51.2; p<0.001; Figure 1). Regarding CGI, the score for disease severity significantly decreased from baseline (mean: 3.8; 95% CI: 3.6–4.0), to the 3-month (mean: 3.0; 95% CI: 2.8–3.2; p<0.001), and 6-month treatment (mean: 2.4; 95% CI: 2.1–2.7; p<0.001).

Changes in SUDs During Vortioxetine Treatment

Compared with baseline, consumption of practically all substances decreased over the 3- and 6-month treatment, especially alcohol (from 35.0 to 23.8% and 17.5%, respectively), cannabis (from 18.8% to 13.8% and 6.3%), and cocaine (from 17.5% to 12.5% and 6.3%; Figure 2). Tobacco use remained stable at baseline and after 3 months (28.8% of patients), while it decreased after 6 months of treatment (25.0%). The severity of the alcohol addiction significantly decreased from baseline (mean: 9.1; 95% CI: 8.0–10.3) to the third month (mean: 6.6; 95% CI: 5.6–7.6; p<0.001), and the sixth month (mean: 4.7; 95% CI: 3.6–5.8; p<0.001; Table 3). Similarly, severity of cannabis addiction reduced

Table 2 Features of Treatments During Vortioxetine Treatment

	Baseline (N=80)	3-Month (N=80)	6-Month (N=80)
Vortioxetine treatment			
Mean dose mg/day (SD)	13.8 (5.5)	14.4 (5.2)	15.1 (5.2)
Doses, n (%)			
5 mg/day	10 (4.2)	6 (2.5)	4 (1.7)
10 mg/día	31 (13.0)	31 (13.0)	29 (12.2)
15 mg/día	7 (2.9)	10 (4.2)	6 (2.5)
20 mg/día	32 (13.5)	33 (13.9)	39 (16.4)
Psychopharmacological-associated treatment, n (%)	73 (91.3)	72 (90.0)	71 (88.8)
Antidepressant drugs	25 (31.3)	24 (30.0)	25 (31.3)
Lithium	1 (1.3)	1 (1.3)	1 (1.3)
Benzodiazepines	29 (36.3)	28 (35.0)	26 (32.5)
Antipsychotics	30 (37.5)	32 (40.0)	31 (38.8)
Antiepileptics	29 (36.3)	25 (31.3)	24 (30.0)
Alcohol Interdictors	11 (13.8)	14 (17.5)	16 (20.0)
Antismoking treatment	0 (0.0)	0 (0.0)	0 (0.0)
Opioid agonists	4 (5.0)	4 (5.0)	4 (5.0)
Opioid antagonists	0 (0.0)	0 (0.0)	0 (0.0)
Acamprosate	0 (0.0)	0 (0.0)	0 (0.0)
Nalmefene	4 (5.0)	3 (3.8)	3 (3.8)
Others	5 (6.3)	6 (7.5)	4 (5.0)
Psychotherapy, n (%)	62 (77.5)	63 (78.8)	63 (78.8)
Individual	36 (58.1)	37 (58.7)	37 (58.7)
Group	4 (6.5)	3 (4.8)	3 (4.8)
Both	22 (35.5)	23 (36.5)	23 (36.5)

Abbreviation: SD, standard deviation.

significantly from baseline (mean: 9.7; 95% CI: 8.3–11.2) to the 3-month (mean: 7.6; 95% CI: 6.2–8.9; p=0.014), and 6-month treatment (mean: 4.1; 95% CI: 2.6–5.6; p<0.001). Decreases in severity were also significant for cocaine (mean: 5.3; 95% CI: 3.7–6.8, versus baseline, mean: 7.4; 95% CI: 5.4–9.3; p=0.022) and sedative-hypnotics (mean: 4.8; 95% CI: 1.4–8.3, versus baseline, mean: 9.2; 95% CI: 4.4–13.9; p=0.080) after 6 months, while a reduction of heroin was observed after 3 months (mean: 6.3; 95% CI: 0.1–12.6, versus baseline, mean: 12.4; 95% CI: 9.7–15.1; p=0.019).

Discussion

We found that vortioxetine is effective in clinical practice for alleviating depressive symptoms and functional impairment, while improving cognitive and executive functions and disease severity for the management of MDD and SUD.

The treatment approach for MDD is changing to cope the heterogeneity of clinical phenotypes and endophenotypes of depression,[5] especially when SUDs is also present. An adequate treatment for patients with both disorders aims at
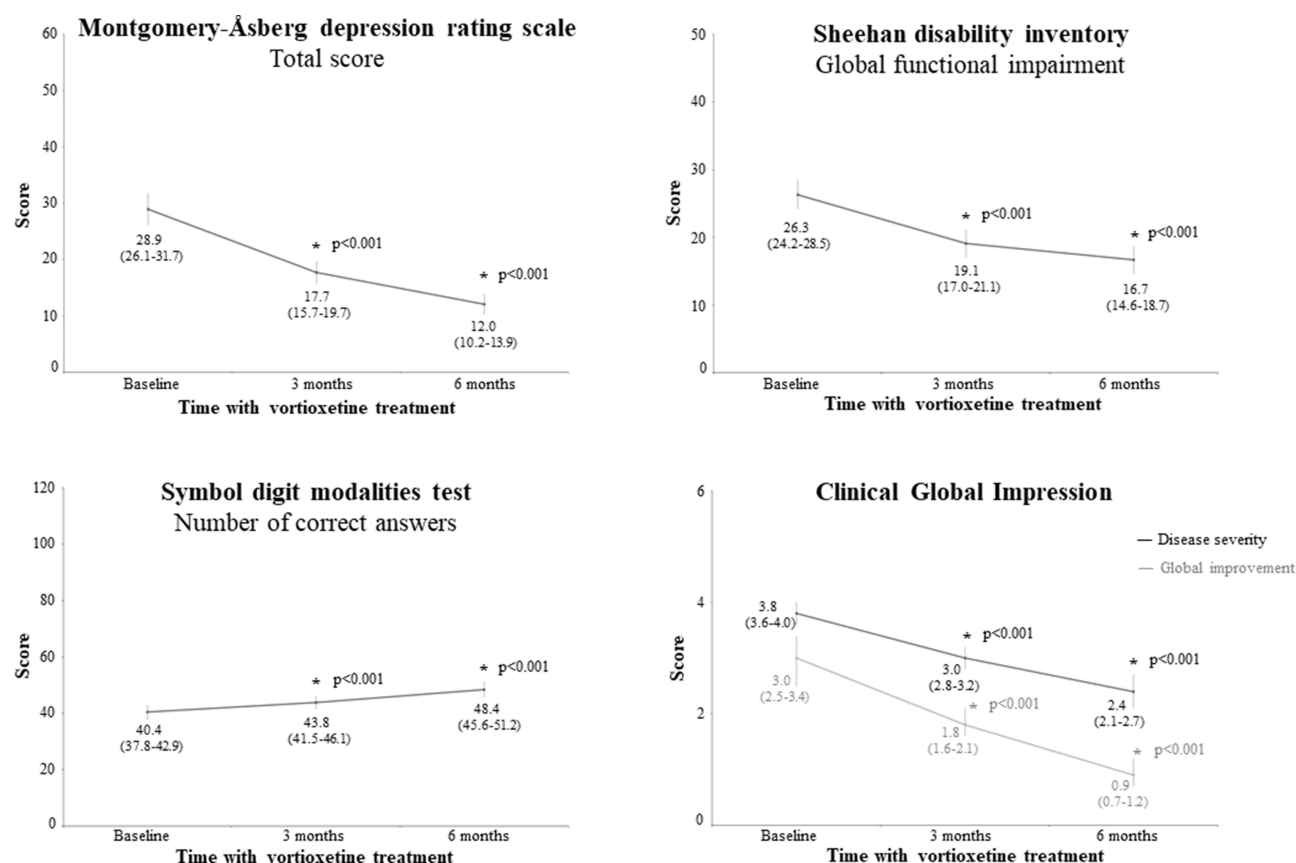
Figure 1 Effect of vortioxetine on evaluated tests at the three time points. Values inside the graphs are the mean and the 95% confidence interval. Asterisks (*) represent statistical significance between baseline and six months of treatment (p<0.001).
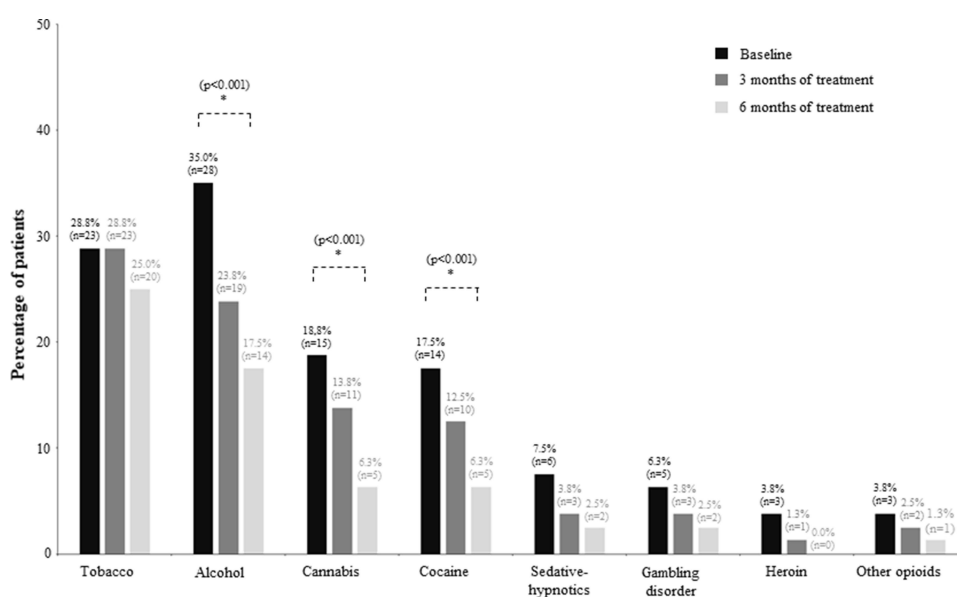

Figure 2 Substance uses during vortioxetine treatment. Asterisks (*) represent statistical significance between baseline and six months of treatment (p<0.001).

improving the depression-related symptoms (including affective, somatic, and cognitive dimensions), reducing the behaviors associated with seeking behaviors and consumption of substances. Additionally, these therapies are also directed to enhance the quality of life and life-satisfaction of patients, and achieve a higher well-being for the family

Table 3 Severity of the Addiction to Substances During Vortioxetine Treatment

	Baseline	3-Month		6-Month	
Severity of Addiction, Mean (95% CI)			p *		p *
Tobacco	8.4 (7.1–9.8)	8.4 (7.6–9.3)	0.920	7.2 (6.2–8.2)	0.157
Alcohol	9.1 (8.0–10.3)	6.6 (5.6–7.6)	<0.001	4.7 (3.6–5.8)	<0.001
Cannabis	9.7 (8.3–11.2)	7.6 (6.2–8.9)	0.014	4.1 (2.6–5.6)	<0.001
Cocaine	7.4 (5.4–9.3)	6.3 (4.9–7.7)	0.262	5.3 (3.7–6.8)	0.022
Sedative-hypnotics	9.2 (4.4–13.9)	7.3 (3.7–11.0)	0.436	4.8 (1.4–8.3)	0.080
Gambling disorder	8.1 (3.8–12.5)	6.1 (3.9–8.4)	0.345	5.3 (2.6–8.0)	0.283
Heroin	12.4 (9.7–15.1)	6.3 (0.1–12.6)	0.019	4.3 (−1.0–9.5)	0.250
Other opioids	8.0 (0.8–15.2)	5.7 (1.9–9.5)	0.346	5.3 (0.2–10.5)	0.392

Note: *Difference with baseline.
Abbreviation: 95% CI, 95% confidence interval.

and society. Vortioxetine, a novel antidepressant drug with a multimodal mechanism of action, has demonstrated its efficacy in the treatment of MDD.[14,15] However, limited number of studies have explored the effectiveness of vortioxetine in real-world settings.[18–20] De Carlo et al[20] evaluated the efficacy, tolerability, and dropout rates of vortioxetine in 66 outpatients with major depressive episodes (45.5% with MDD diagnosis) at three time points. Authors reported significant improvements in scores of all evaluated tests (CGI efficacy index, Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale; MADRS, and Young Mania Rating Scale). Regarding MADRS, scores significantly decreased from baseline (24.5 ± 5.7) to the first (19.5 ± 6.4) and second (14.9 ± 7.6; p<0.001) time points. Responses to the treatment and remission rates were reported in 51.5% and 36.4% of patients, respectively. Similarly, Chin et al[18] assessed the evolution of MDD in 138 patients receiving vortioxetine for three months in real-world settings. Significant reductions were reported during the treatment in depression severity (using the Patient Health Questionnaire-9, 18.7 ± 5.7 versus 5.0 ± 5.3), CGI-severity score (4.4 ± 0.7 versus 2.2 ± 1.1), and cognitive function (using the perceived deficit questionnaire–depression, 42.1 ± 18.8 versus 13.4 ± 13.0), in comparison to the baseline. Response to the treatment and remission rates were achieved in 80.8% and 59.0% of patients, respectively.

Despite the large proportion of patients with MDD having concurrent SUDs, yielding a higher risk of suicide, greater social and personal impairment, and other psychiatric conditions,[6] only a sole study using vortioxetine has evaluated its effectiveness on these patients.[21] Di Nicola et al[21] described 45.6% and 22.8% of remission and response rates in patients with MDD and AUD. Moreover, 1.8% and 3.5% of patients being non-responders and experiencing a relapse, respectively. Indeed, patients with SUDs are frequently excluded from antidepressant efficacy trials for avoiding confounding results and the development of serious adverse events.[29] The goal of our study was thus to provide the experience of vortioxetine in routine clinical practice on a cohort of patients with major MDD and SUD. Our results are in agreement with other real-world studies using vortioxetine.[18–20] Scores for depression scale (MADRS) and functional impairment (SDI) significantly decreased during the treatment, while cognitive and executive functions (SDMT), and disease severity (CGI) significantly improved. Similar results were obtained in FOCUS,[31,32] and CONNECT clinical trials.[33,34] The randomized, double-blind, placebo-controlled FOCUS study analyzed the efficacy of vortioxetine (10 or 20 mg/day) in cognitive function and depressive symptoms of 602 adults.[29] A post-hoc analysis of the FOCUS trial assessed changes in cognitive function of MDD working patients treated with vortioxetine. Both analyses highlighted that vortioxetine improved cognitive functions, independently of the alleviation of depressive symptoms. In the multicenter, randomized, double-blind, placebo-controlled, CONNECT study,[33] vortioxetine significantly improved cognitive function and functionality, and decreased depression rates. Furthermore, in a cost-effectiveness study of vortioxetine versus duloxetine

with patients from CONNECT study, authors suggested that vortioxetine may be a more adequate cost-effective alternative to duloxetine due to its superior ability to improve functional capacities.[34] Therefore, both FOCUS and CONNECT trials evidenced the clinical benefit of vortioxetine on cognitive function in MDD. Moreover, Liebowitz et al,[35] in a 12-week double-blind, placebo-controlled trial, evaluated the efficacy of vortioxetine in 40 patients with MDD and social anxiety disorder. Patients receiving vortioxetine showed significantly greater improvements on MADRS (effect size 0.7) and Liebowitz Social Anxiety Scale (effect size 0.7), compared to placebo. Pettinati et al,[36] in a review of eight randomized, controlled trials of treatment for depression with alcohol use disorder, found that some of the antidepressants were effective in reducing depressive symptoms, however they had a mild effect in reducing alcohol use. In our study, substance use and severity of addiction was reduced significantly during vortioxetine treatment, especially for alcohol, cannabis, and cocaine.

The main limitation of the study was its retrospective nature, providing only the available information on medical charts. Additionally, it was a naturalistic study, so no comparisons were made towards a control group. Moreover, the number of patients was relatively low. In addition, while both CGI severity and improvement scales are a readily understood and practical measurement tool that can easily be administered by clinicians, among its frequently mentioned limitations the lack of well-defined behavioral anchors is included. As a result, the scoring mainly depends on the experience and judgement of the clinician, resulting in a poor inter-inter reliability. Additional criticisms include the absence of extensive psychometric validation, the inclusion of redundant information and being overly reliant on the memory of the clinician.[37–40] Finally, no efforts were made to address potential sources of bias, which might represent a methodological limitation of the study. Besides this, our observations are in line with other real-world studies and clinical trials. On the other hand, main strengths of the study included that it was performed in real-world settings, and evaluated depression and SUD simultaneously. Real-world studies on vortioxetine are limited,[18–20] thus the present study provides additional and positive evidence about its use, especially for MDD and SUD.

Conclusions

Vortioxetine was effective in clinical practice for reducing depression symptoms and functional impairment and improving cognitive and executive functions and disease severity in patients with MDD and SUD. Moreover, the treatment with vortioxetine favored a reduction in substance use and the severity of the SUDs. Further prospective, long-term studies, including larger cohort of patients, are required to corroborate these results.

Abbreviations

CGI, clinical global impression; CI95%, 95% confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SDI, Sheehan Disability Inventory; SDMT, symbol digit modalities test; SNRI, serotonin-noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; SUD, substance use disorder.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of the Gregorio Marañon University Hospital (Madrid, Spain), with the reference number FPD-VOR-2019-01.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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