Received: 2 January 2020 | Revised: 16 April 2020 | Accepted: 3 June 2020

DOI: 10.1002/hup.2750



RESEARCH ARTICLE

WILEY

# Effectiveness, tolerability, and dropout rates of vortioxetine in comorbid depression: A naturalistic study

Vera De Carlo[1] | Matteo Vismara[1] | Benedetta Grancini[1] | Beatrice Benatti[1] | Monica Francesca Bosi[1] | Anna Colombo[1] | Caterina Adele Viganò[1] | Bernardo Dell'Osso[1,2,3]

[1]Department of Biomedical and Clinical Sciences "Luigi Sacco", Psychiatriy Clinic, Ospedale Sacco-Polo Universitario-ASST Fatebenefratelli-Sacco, University of Milan, Milan, Italy

[2]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA

[3]"Aldo Ravelli" Center for Neurotechnology and Brain Therapeutic, University of Milan, Milan, Italy

**Correspondence**
Vera De Carlo, Department of Biomedical and Clinical Sciences "Luigi Sacco", Psychiatriy clinic, Ospedale Sacco-Polo Universitario-ASST Fatebenefratelli-Sacco, University of Milan, Via Giovanni Battista Grassi, 74, 20157 Milan, Italy.
Email: vera.decarlo@unimi.it

## Abstract

**Objective:** Vortioxetine is a novel antidepressant whose safety, tolerability, and therapeutic action have been supported by several studies. The present naturalistic study aimed to characterize its effectiveness, tolerability, and dropout rate in the real world.

**Methods:** Total sample consisted of 66 outpatients with major depressive episode, treated with vortioxetine, whose clinical variables were evaluated over three time points.

**Results:** Most common primary diagnoses were major depressive disorder (45.5%) and bipolar disorder (33.4%), with an overall comorbidity rate of 48.5% and concomitant medications in the 89.4%. The mean vortioxetine daily dosage was 12.90 ± 5.65 mg. Effectiveness of vortioxetine through a significant improvement on specific psychometric scales emerged, while only a nonsignificant trend of association between higher dosage and effectiveness was found. In the total sample, 51.5% were classified as responders and 36.4% as remitters. Two-thirds of subjects did not report side effects, while in the remaining patients, gastrointestinal ones were the most frequent (72.7%). Almost two-thirds of the sample could complete the follow-up, while 36.4% dropped out; the main reasons for dropout were side effects (37.5%) and lack of efficacy (29.2%).

**Conclusions:** Larger sample studies are warranted to better characterize vortioxetine effectiveness and tolerability in the real world.

KEYWORDS
affective disorders, dropout, effectiveness, tolerability, vortioxetine

## 1 | INTRODUCTION

Major depressive disorder (MDD) is a prevalent, burdensome, and frequently comorbid psychiatric condition (Charara et al., 2017), associated with reduced quality of life and impaired cognitive functioning (Corruble & Guelfi, 2000; Papakostas, 2014).

Despite several compounds being approved for the treatment of MDD, roughly half of affected patients report an inadequate response to first-line antidepressant treatment (Papakostas, Nielsen, Dragheim, & Tonnoir, 2018). Moreover, even though antidepressants represent the cornerstone in the treatment of MDD, available therapies often show several side effects (Rizvi & Kennedy, 2011).

The present study was conducted according to the principles expressed in the Declaration of Helsinki.

Consequently, many depressed patients fail to remit after an initial antidepressant trial, often deciding to stop treatment and requiring an additional treatment switch (Rush et al., 2006). With respect to bipolar depression, this represents the most pervasive and difficult to treat phase of bipolar disorder (Galimberti et al., 2019), and even though the utility of antidepressants in bipolar depression is still debated, they are largely used as augmentative agents for the treatment of bipolar depression (Dell'Osso et al., 2020). Ultimately, depressive episodes often occur in other psychiatric disorders (i.e., personality disorders [PerDs] or eating disorders [EDs], or obsessive compulsive disorder [OCD]) as comorbidity and could complicate the course of primary illness (De Carlo, Calati, & Serretti, 2016; Lochner et al., 2014; Zheng et al., 2019).

New generations of antidepressants aim at optimizing treatment efficacy and tolerability. Vortioxetine, for instance, is a novel antidepressant with multimodal activity (Papakostas et al., 2018), approved for the treatment of MDD in the last decade in many countries worldwide (European Medicines Agency [EMA], 2014; Food and Drug Administration [FDA], 2013). Its mechanism of action combines the inhibition of the serotonin transporter and the direct modulation of serotonin (5-HT) receptor activity, being it a 5-HT1A receptor agonist, a 5-HT1B receptor partial agonist, a 5-HT3, a 5-HT7, and a 5-HT1D receptor antagonist and an inhibitor of the 5-HT transporter (Bang-Andersen et al., 2011). The safety, tolerability, and therapeutic action of vortioxetine over affective symptoms have been addressed by several studies (Berhan & Barker, 2014; Jacobsen, Harper, Chrones, Chan, & Mahableshwarkar, 2015), conducted with low (up to 10 mg/day) (Alam, Jacobsen, Chen, Serenko, & Mahableshwarkar, 2014; Baldwin, Hansen, & Florea, 2012) and higher dosages (15–20 mg/day) (Jacobsen, Mahableshwarkar, Serenko, Chan, & Trivedi, 2015). Moreover, this compound was found to be able to improve some aspects of cognitive dysfunction associated with depression (Atique-Ur-Rehman & Neill, 2019; Pehrson et al., 2015), due to its ability to modulate a wide range of neurotransmitters (Salagre, Grande, Solé, Sanchez-Moreno, & Vieta, 2018). Furthermore, the side effects of vortioxetine differ from those of other antidepressants, according to the low incidence of sexual dysfunction and weight gain (Salagre et al., 2018). Conversely, reports of gastrointestinal side effects, particularly nausea, seem to be highly associated with vortioxetine, mainly at the beginning of the treatment (Hughes, Lacasse, Fuller, & Spaulding-Givens, 2017).

In the available literature, there is a limited amount of real-world studies evaluating potential differences in terms of effectiveness, tolerability, and dropout rate between patients treated with low versus higher daily doses of vortioxetine.

Therefore, the present naturalistic study aimed to characterize effectiveness and tolerability of vortioxetine in the real world, focusing on discontinuation rates and related reasons, in a sample of patients with other psychiatric and medical comorbidities, receiving mono- and polytherapies and different dosages of vortioxetine.

Given that investigation of the aforementioned variables in the real world is substantially limited, we did not formulate any a priori hypothesis, in terms of effectiveness, tolerability, and dropout rates in the total sample and across differential low versus higher dosage groups, also considering that vortioxetine was frequently administered in patients with polycomorbidity, polytherapy, long duration of illness, and previous exposure to other antidepressants.

## 2 | MATERIAL AND METHODS

### 2.1 | Sample selection

For the present observational study, 66 patients attending the psychiatric outpatient service of the Department of Mental Health of the "Ospedale Luigi Sacco" in Milan (Italy) were recruited.

After receiving a full explanation of the protocol, all patients gave their informed consent for participating in the study.

Data were gathered directly from patients, assessed by psychiatrists or residents in psychiatry with specific training in mood disorder management, through the Structured Clinical Interviews for DSM-5, clinical version (First, Williams, Karg, & Spitzer, 2016) and the Structured Clinical Interview for DSM-5, Personality Disorder (First, Williams, Benjamin, & Spitzer, 2015), in order to ascertain psychiatric diagnoses and comorbidities, or through a retrospective review of patients' medical records from October 2015 to February 2019. In some cases, the interview took place with the presence of patients' relatives or caregivers, with their consent.

Eligible patients were adults (over age 18 years), with an ongoing major depressive episode (MDE), according to the DSM-5 criteria (American Psychiatric Association, 2013) at the moment of the first vortioxetine prescription. The MDE could be related to a primary diagnosis of MDD or represent a comorbid condition. Indeed, patients could have a primary diagnosis of affective disorders (i.e., MDD, bipolar disorder [BD] 1 or BD 2), anxiety disorders (generalized anxiety disorder [GAD] and panic disorder [PD]), obsessive-compulsive disorder, personality disorders, or another primary diagnosis (adjustment disorders [ADs] and EDs). Exclusion criteria included the following: age <18 years old, the presence of brain diseases, mental retardation, and psychiatric disorders secondary to a medical condition. Patients with different dosages of vortioxetine (in the range of 5–20 mg/day), different titration approaches, and different regimens in terms of unique versus multiple daily administration were included. Sociodemographic and clinical variables included the following: gender, age, age at onset, duration of illness, duration of untreated illness (DUI, defined as the time interval, in months, elapsing between the onset of the disorder and the administration of the first pharmacological treatment, in compliant patients, at an appropriate dosage and for an adequate period of time, in agreement with recently updated International Treatment Guidelines) (Bauer et al., 2013; Grunze et al., 2013), primary psychiatric diagnosis, psychiatric and medical comorbidities, psychiatric family history, prevalence and lifetime number of hospitalization, dosage and side effects of vortioxetine, and associated polytherapy.

## 2.2 | Assessment

Three subsequent evaluations were conducted; the first one of which taking place when vortioxetine was started (T0), then respectively 4 weeks (T1) after the effective dose (evaluated according to clinical judgment) was reached, and then after 8 weeks from T1 (T2). The following psychometric scales were administered: Hamilton Depression Rating Scale-21 items (HAM-D-21) (Hamilton, 1967), Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978), and Clinical Global Impression (CGI)–Efficacy Index (Guy, 1976). To assess side effects, the questionnaires Dosage Record Treatment Emergent Symptom Scale (DOTES) (Guy, 1976) and Treatment Emergent Symptoms Write-In Scale (TWIS) were used. We considered as response ≥50% decrease of HAM-D total score at T1 or T2, while as remission HAMD ≤7 total score (De Carlo et al., 2016) at T2. Dropouts at T2 were not taken into account for statistical analysis related to remission rates, while dropouts at T1 were excluded for analysis on response rate.

## 2.3 | Statistical analysis

At first, descriptive analyses of sociodemographic and clinical variables of the total sample were performed. Effectiveness was assessed using repeated measures analysis of variance (ANOVA) for psychometric scales, carried out on the total sample and across different groups with respect to dosage, associated therapy (considered as dichotomous variables, i.e., antidepressants yes vs. no, stabilizers yes vs. no, benzodiazepines yes vs. no, and antipsychotics yes vs. no), and comorbid psychiatric or medical conditions (considered as dichotomous variables). In case of a missing outcome value, due to dropout, the last observation was carried forward (LOCF analysis) for the qualitative analysis. Moreover, response and remission rates in the total sample and across different groups of dosage were investigated. The correlation between study outcomes (i.e., response and remission rates, dropout rates, and side effects) and sociodemographic and clinical variables was investigated using $\chi^2$ tests for categorical variables and *t*-test for continuous ones. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 19.

# 3 | RESULTS

## 3.1 | Sample description

The main sociodemographic and clinical variables of the study sample ($n = 66$) are summarized in Table 1.

The sample showed a mean age of 35.26 ± 16.31 years and a gender distribution of 36.4% men and 63.6% women. The mean DUI of the total sample was 36.70 ± 66.35 months, the mean age at illness onset was 35.26 ± 16.31 years, and the mean duration of illness was 15.02 ± 10.42 years.

Most common primary diagnoses were MDD (45.5%) and BD (33.4%), with an overall comorbidity rate of 48.5% in the overall sample. The 31.8% of the recruited patients reported at least one lifetime hospitalization.

Associated medications were present in the 89.4% of the total sample and remained stable across the follow-up. Furthermore, the 87.9% of the patients had been previously treated with other antidepressants.

The total sample showed a mean vortioxetine daily dosage of 12.90 ± 5.65 mg (range 5–20 mg), and the 33.3% ($N = 22$) of the total sample could reach the highest dose of 20 mg/day.

## 3.2 | Effectiveness

Repeated measures ANOVA highlighted a significant improvement of HAM-D, MADRS, HAM-A, YMRS, and CGI–efficacy index across time (Table 2 and Figure 1a). No significant differences emerged from a comparison between groups of patients treated with different daily dosages of vortioxetine (≤10 mg vs. >10 mg, <15 mg vs. ≥15 mg, 20 mg vs. other dosage, and 20 mg vs. ≤10 mg), in terms of effectiveness (Table 2). However, a statistically nonsignificant trend of association between increasing dosages of vortioxetine and higher improvements on psychometric scales was observed. Moreover, no significant differences in scales improvement emerged considering the presence of a comorbid psychiatric or medical disease or concurrent medication. Response and remission rates of 51.5% ($N = 34/57$) and 36.4% ($N = 24/42$), respectively, were found in the total sample, without any significant difference, comparing different groups of daily dosages (Table 3 and Figure 1b). Finally, no correlation between response and remission rates and sociodemographic or clinical variables emerged.

## 3.3 | Tolerability

Two-thirds of the total sample could tolerate vortioxetine without reporting any side effect. Side effects were reported by 33.3% of the total sample: respectively represented by gastrointestinal side effects (mainly nausea, vomit, and diarrhea) in the 72.7% of them and gastrointestinal side effects associated with other side effects (mainly headache and sweating) in the 22.7% of them. Mean duration of side effects was 37.17 ± 33.12 days with moderate–severe (72.8%) or mild (27.3%) severity, measured through the DOTES and the TWIS. The association between reported side effects and vortioxetine was considered probable in the 90.9% of patients, remote, or only possible in the rest of the sample on the basis of TWIS. Comparative analyses did not show any differences in terms of tolerability across distinct dosage groups and any correlation with other sociodemographic or clinical variables.

**TABLE 1** Main sociodemographic and clinical features of the study sample and profile of vortioxetine tolerability

| Total sample ($N = 66$) | | |
|---|---|---|
| Gender | Male | 36.4% ($N = 24$) |
| | Female | 63.6% ($N = 42$) |
| Age (years) | 50.20 ± 15.81 | |
| Age at onset (years) | 35.26 ± 16.31 | |
| Vortioxetine dosage | 12.9 ± 5.65 mg | |
| | 20 mg | 33.3% ($N = 22$) |
| | <15 mg | 57.58% ($N = 38$) |
| | ≥15 mg | 42.42% ($N = 28$) |
| | ≤10 mg | 56.1% ($N = 37$) |
| | >10 mg | 43.9% ($N = 29$) |
| Psychiatric primary diagnosis | MDD | 45.5% ($N = 30$) |
| | BD 1 | 7.6% ($N = 5$) |
| | BD 2 | 25.8% ($N = 17$) |
| | GAD | 7.6% ($N = 5$) |
| | PD | 3.0% ($N = 2$) |
| | OCD | 4.5% ($N = 3$) |
| | PerD | 1.5% ($N = 1$) |
| | Other | 4.5% ($N = 3$) |
| Psychiatric family history | Yes | 62.1% ($N = 41$) |
| | No | 37.9% ($N = 25$) |
| Psychiatric comorbidities | Yes | 48.5% ($N = 32$) |
| | No | 51.5% ($N = 34$) |
| Medical comorbidity | Yes | 62.1% ($N = 41$) |
| | No | 37.9% ($N = 25$) |
| Hospitalization | Yes | 31.8% ($N = 21$) |
| | No | 68.2% ($N = 45$) |
| Psychiatric comorbidity | None | $N = 34$ (51.5%) |
| | MDD | $N = 4$ (6.1%) |
| | GAD | $N = 6$ (9.1%) |
| | PD | $N = 2$ (3.0%) |
| | OCD | $N = 1$ (1.5%) |
| | PerD | $N = 8$ (12.1%) |
| | ED | $N = 1$ (1.5%) |
| | AD | $N = 1$ (2.1%) |
| | Substance/Alcohol/ BDZ abuse | $N = 4$ (6.1%) |
| | Polycomorbidity | $N = 4$ (6.1%) |
| Associated therapy[a] | Antidepressants yes/no | 33.3% ($N = 22$) |
| | Stabilizers yes/no | 54.5% ($N = 36$) |
| | Benzodiazepines yes/no | 37.9% ($N = 25$) |
| | Antipsychotics yes/no | 51.5% ($N = 34$) |
| SEs | Yes | 33.3% ($N = 22$) |
| | No | 66.7% ($N = 44$) |
| SE duration | 37.17 ± 33.12 days | |
| SE association (DOTES-TWIS) | Remote | 4.5% ($N = 1$) |
| | Possible | 4.5% ($N = 1$) |
| | Probable | 90.9% ($N = 20$) |
| SE severity | Mild | 27.3% ($N = 6$) |
| | Moderate | 36.4% ($N = 8$) |
| | Severe | 36.4% ($N = 8$) |
| Type of SE[b] | GI | 72.7% ($N = 16$) |
| | ↓ Libido | 4.5% ($N = 1$) |
| | GI + other | 22.7% ($N = 5$) |
| Dropout | Yes | 36.4% ($N = 24$) |
| | No | 63.6% ($N = 42$) |
| Reasons of dropout | SEs | 37.5% ($N = 9$) |
| | Noneficacy | 29.2% ($N = 7$) |
| | Manic switch | 12.5% ($N = 3$) |
| | Others | 8.3% ($N = 2$) |
| | >1 reason | 12.5% ($N = 3$) |
| DUI (months) | 36.70 ± 66.35 | |
| Previous antidepressant | Yes | 87.9% ($N = 58$) |
| | No | 12.1% ($N = 8$) |
| Duration of illness (years) | 15.02 ± 10.42 | |
| Medical comorbidity | None | $N = 25$ (37.9%) |
| | Hypertension | $N = 1$ (1.5%) |
| | Diabetes | $N = 1$ (1.5%) |
| | Dysthyroidism | $N = 4$ (6.1%) |
| | Dyslipidemia | $N = 4$ (6.1%) |
| | Other | $N = 17$ (25.8%) |
| | Polycomorbidity | $N = 14$ (21.2%) |
| Response rate[c] | 51.5% ($N = 34$) | |
| Remission rate[c] | 36.4% ($N = 24$) | |

*Note*: Values are represented as mean ± SD.

Abbreviations: AD, adjustment disorder; BD, bipolar disorder; BDZ, benzodiazepines; DUI, duration of untreated illness; ED, eating disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PD, panic disorder; PerD, personality disorder; SE, side effect.

[a]The total percentage could exceed 100, because the same patient could have different associated treatments.

[b]Percentages are related to the total of 22 patients reporting side effects (33.3% of the total sample).

[c]Dropouts at T1 were not taken into account for statistical analysis related to remission rates, while dropouts both at T1 and T2 were excluded for analysis on response rate.

**TABLE 2** Psychometric evaluation across time points for the total sample and different dosage subgroups

| | | *N* | T0 | T1 | T2 | *p* |
|---|---|---|---|---|---|---|
| HAM-D | Total sample | 66 | 20.17 ± 5.77 | 15.55 ± 6.17 | 11.30 ± 7.10 | 0.000 |
| | Vortioxetine ≤ 10 mg | 37 | 20.68 ± 5.83 | 15.22 ± 6.12 | 11.30 ± 7.67 | 0.947 |
| | Vortioxetine > 10 mg | 29 | 19.52 ± 5.74 | 15.97 ± 6.32 | 11.31 ± 6.43 | |
| | Vortioxetine < 15 mg | 38 | 20.53 ± 5.82 | 15.37 ± 6.11 | 11.55 ± 7.72 | 0.688 |
| | Vortioxetine ≥ 15 mg | 28 | 19.68 ± 5.77 | 16.00 ± 6.43 | 11.18 ± 6.50 | |
| | Vortioxetine 20 mg | 22 | 18.68 ± 3.90 | 14.77 ± 4.05 | 9.95 ± 5.69 | 0.693 |
| | Vortioxetine < 20 mg | 44 | 20.91 ± 5.77 | 16.07 ± 7.04 | 12.11 ± 78 | |
| | Vortioxetine 20 mg | 22 | 18.68 ± 3.90 | 14.77 ± 4.05 | 9.95 ± 5.69 | 0.683 |
| | Vortioxetine ≤ 10 mg | 37 | 20.68 ± 5.83 | 15.38 ± 6.19 | 11.46 ± 7.81 | |
| | Vortioxetine = single AD | 44 | 20.39 ± 6.19 | 16.25 ± 4.47 | 11.73 ± 7.31 | 0.692 |
| | Vortioxetine + other AD | 22 | 19.73 ± 4.94 | 14.41 ± 5.57 | 10.73 ± 7.05 | |
| MADRS | Total sample | 66 | 24.53 ± 5.71 | 19.50 ± 6.35 | 14.88 ± 7.64 | 0.000 |
| | Vortioxetine ≤ 10 mg | 37 | 24.59 ± 5.97 | 18.54 ± 6.44 | 14.24 ± 8.08 | 0.714 |
| | Vortioxetine > 10 mg | 29 | 24.45 ± 5.46 | 20.72 ± 6.11 | 15.69 ± 7.10 | |
| | Vortioxetine < 15 mg | 38 | 24.55 ± 5.90 | 18.63 ± 6.38 | 14.45 ± 8.07 | 0.713 |
| | Vortioxetine ≥ 15 mg | 28 | 24.53 ± 5.71 | 20.68 ± 6.22 | 15.46 ± 7.12 | |
| | Vortioxetine 20 mg | 22 | 23.73 ± 4.10 | 19.68 ± 4.28 | 14.23 ± 6.82 | 0.717 |
| | Vortioxetine < 20 mg | 44 | 24.53 ± 6.37 | 19.41 ± 7.20 | 15.20 ± 8.08 | |
| | Vortioxetine 20 mg | 22 | 23.73 ± 4.10 | 19.68 ± 4.28 | 14.23 ± 6.82 | 0.708 |
| | Vortioxetine ≤ 10 mg | 37 | 24.59 ± 5.97 | 18.54 ± 6.44 | 14.24 ± 8.08 | |
| | Vortioxetine = single AD | 44 | 24.98 ± 5.94 | 20.48 ± 6.32 | 15.39 ± 7.91 | 0.715 |
| | Vortioxetine + other AD | 22 | 23.64 ± 5.22 | 17.55 ± 6.06 | 13.86 ± 7.15 | |
| HAM-A | Total sample | 66 | 14.83 ± 5.27 | 11.65 ± 5.26 | 8.62 ± 5.62 | 0.000 |
| | Vortioxetine ≤ 10 mg | 37 | 14.86 ± 5.38 | 11.32 ± 5.01 | 8.46 ± 5.87 | 0.761 |
| | Vortioxetine > 10 mg | 29 | 14.79 ± 5.22 | 12.07 ± 5.62 | 8.83 ± 5.38 | |
| | Vortioxetine < 15 mg | 38 | 14.76 ± 5.35 | 11.32 ± 4.94 | 8.53 ± 5.81 | 0.729 |
| | Vortioxetine ≥ 15 mg | 28 | 14.93 ± 5.27 | 12.11 ± 5.72 | 8.75 ± 5.46 | |
| | Vortioxetine 20 mg | 22 | 14.00 ± 4.45 | 10.82 ± 4.48 | 7.59 ± 4.62 | 0.732 |
| | Vortioxetine < 20 mg | 44 | 15.25 ± 5.64 | 12.07 ± 5.61 | 9.14 ± 6.05 | |
| | Vortioxetine 20 mg | 22 | 14.00 ± 4.45 | 10.82 ± 4.48 | 7.59 ± 4.62 | 0.726 |
| | Vortioxetine ≤ 10 mg | 37 | 14.86 ± 5.38 | 11.32 ± 5.01 | 8.46 ± 5.87 | |
| | Vortioxetine = single AD | 44 | 15.25 ± 5.45 | 12.23 ± 5.37 | 8.84 ± 5.54 | 0.729 |
| | Vortioxetine + other AD | 22 | 14.00 ± 4.91 | 10.50 ± 4.95 | 8.18 ± 5.89 | |
| YMRS | Total sample | 66 | 2.65 ± 1.52 | 2.27 ± 1.87 | 1.71 ± 1.92 | 0.000 |
| | Vortioxetine ≤ 10 mg | 37 | 2.76 ± 1.55 | 2.38 ± 2.11 | 1.78 ± 2.25 | 0.976 |
| | Vortioxetine > 10 mg | 29 | 2.52 ± 1.50 | 2.14 ± 1.53 | 1.62 ± 1.43 | |
| | Vortioxetine < 15 mg | 38 | 2.68 ± 1.60 | 2.32 ± 2.12 | 1.74 ± 2.24 | 0.729 |
| | Vortioxetine ≥ 15 mg | 28 | 2.61 ± 1.45 | 2.21 ± 1.50 | 1.75 ± 1.38 | |
| | Vortioxetine 20 mg | 22 | 2.58 ± 1.37 | 2.18 ± 1.47 | 1.73 ± 1.39 | 0.729 |
| | Vortioxetine < 20 mg | 44 | 2.68 ± 1.61 | 2.32 ± 2.06 | 1.75 ± 1.14 | |

(Continues)

TABLE 2 (Continued)

| | | N | T0 | T1 | T2 | p |
|---|---|---|---|---|---|---|
| YMRS | Vortioxetine 20 mg | 22 | 2.58 ± 1.37 | 2.18 ± 1.47 | 1.73 ± 1.39 | 0.721 |
| | Vortioxetine ≤ 10 mg | 37 | 2.76 ± 1.55 | 2.38 ± 2.11 | 1.78 ± 2.25 | |
| | Vortioxetine = single AD | 44 | 2.77 ± 1.61 | 2.50 ± 2.11 | 1.98 ± 2.18 | 0.732 |
| | Vortioxetine + other AD | 22 | 2.41 ± 1.33 | 1.82 ± 1.18 | 1.27 ± 1.08 | |
| CGI-efficacy index | Total sample | 66 | - | 1.75 ± 1.19 | 2.35 ± 1.58 | 0.000 |
| | Vortioxetine ≤ 10 mg | 37 | - | 1.74 ± 1.34 | 2.32 ± 1.68 | 0.973 |
| | Vortioxetine > 10 mg | 29 | - | 1.75 ± 0.99 | 2.39 ± 1.48 | |
| | Vortioxetine < 15 mg | 38 | - | 1.72 ± 1.32 | 1.77 ± 0.99 | 0.803 |
| | Vortioxetine ≥ 15 mg | 28 | - | 2.29 ± 1.67 | 2.48 ± 1.48 | |
| | Vortioxetine 20 mg | 22 | - | 1.91 ± 0.97 | 2.64 ± 1.43 | 0.806 |
| | Vortioxetine < 20 mg | 44 | - | 1.66 ± 1.29 | 2.24 ± 1.65 | |
| | Vortioxetine 20 mg | 22 | - | 1.91 ± 0.97 | 2.64 ± 1.43 | 0.830 |
| | Vortioxetine ≤ 10 mg | 37 | - | 1.74 ± 1.34 | 2.32 ± 1.68 | |
| | Vortioxetine = single AD | 44 | - | 1.75 ± 1.15 | 2.41 ± 1.57 | 0.802 |
| | Vortioxetine + other AD | 22 | - | 1.74 ± 1.28 | 2.29 ± 1.64 | |

*Note*: 'Vortioxetine = single AD': patients treated with vortioxetine as single antidepressant (in association with other psychopharmacological class or not). 'Vortioxetine + other AD': patients treated with vortioxetine together with other antidepressants (in association with other psychopharmacological class or not).

Abbreviations: CGI, clinical global impression; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

### 3.4 | Dropouts

Almost two-thirds of the total sample could complete the entire follow-up. Approximately one-third of the total sample (36.4%, $N = 24$) dropped out, respectively, 13.6% at T1 and 22.8% at T2. The reasons for dropout were side effects (37.5%), lack of efficacy (29.2%), manic switch (12.5%), more than one reason (12.5%), and others (e.g., personal decision, 8.3%). Therefore, in the 37.5% of the dropouts, treatment needed to be stopped because of low tolerability issues. These data are reported in Table 1 and represented in Figure 2a,b. Moreover, after splitting dropouts in two additional subgroups (at T1 and T2), it was found that most of the patients dropping out at T1, discontinued for side effects (62.5%), while considering dropouts at T2, the main reason of discontinuation was lack of efficacy (37.5%), followed by persistence of side effects (25.0%). No statistically significant correlation between dropout rate and different dosages and other sociodemographic and clinical variables emerged.

## 4 | DISCUSSION

The present naturalistic study aimed to characterize effectiveness, tolerability, and dropout rates of vortioxetine in a sample of patients with an MDE in the real world (e.g., with comorbidities and concomitant treatments).

### 4.1 | Effectiveness

An overall significant improvement of HAM-D, MADRS, HAM-A, YMRS, and CGI–efficacy index across time points was observed, in line with the available literature (Baldwin et al., 2016; Baldwin, Florea, Jacobsen, Zhong, & Nomikos, 2016; Nomikos, Tomori, Zhong, Affinito, & Palo, 2017). In particular, in a systematic review and network meta-analysis, comparing efficacy and acceptability of 21 antidepressant drugs, vortioxetine, together with agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, and venlafaxine were found to be more effective than other assessed antidepressants (Cipriani et al., 2018). However, studies specifically examining the effectiveness of vortioxetine in the real world are limited (Alvarez, Perez, Dragheim, Loft, & Artigas, 2012; Baldwin, Loft, & Dragheim, 2012; Boulenger, Loft, & Olsen, 2014; Henigsberg, Mahableshwarkar, Jacobsen, Chen, & Thase, 2012; Jain, Mahableshwarkar, Jacobsen, Chen, & Thase, 2013; Katona, Hansen, & Olsen, 2012; Mahableshwarkar, Jacobsen, & Chen, 2013; Pae et al., 2015). Therefore, the specific purpose of the present study was to characterize the effectiveness profile of vortioxetine in a real-world sample of patients with polycomorbidity, polytherapy, long duration of illness, and previous exposure to other antidepressants. Indeed, in our sample, most of the patients were taking an additional medication, including a different antidepressant, although no correlation between effectiveness and concurrent medications or the use of a previous antidepressant emerged. Moreover, in terms of vortioxetine dosage, no significant differences resulted from a comparison

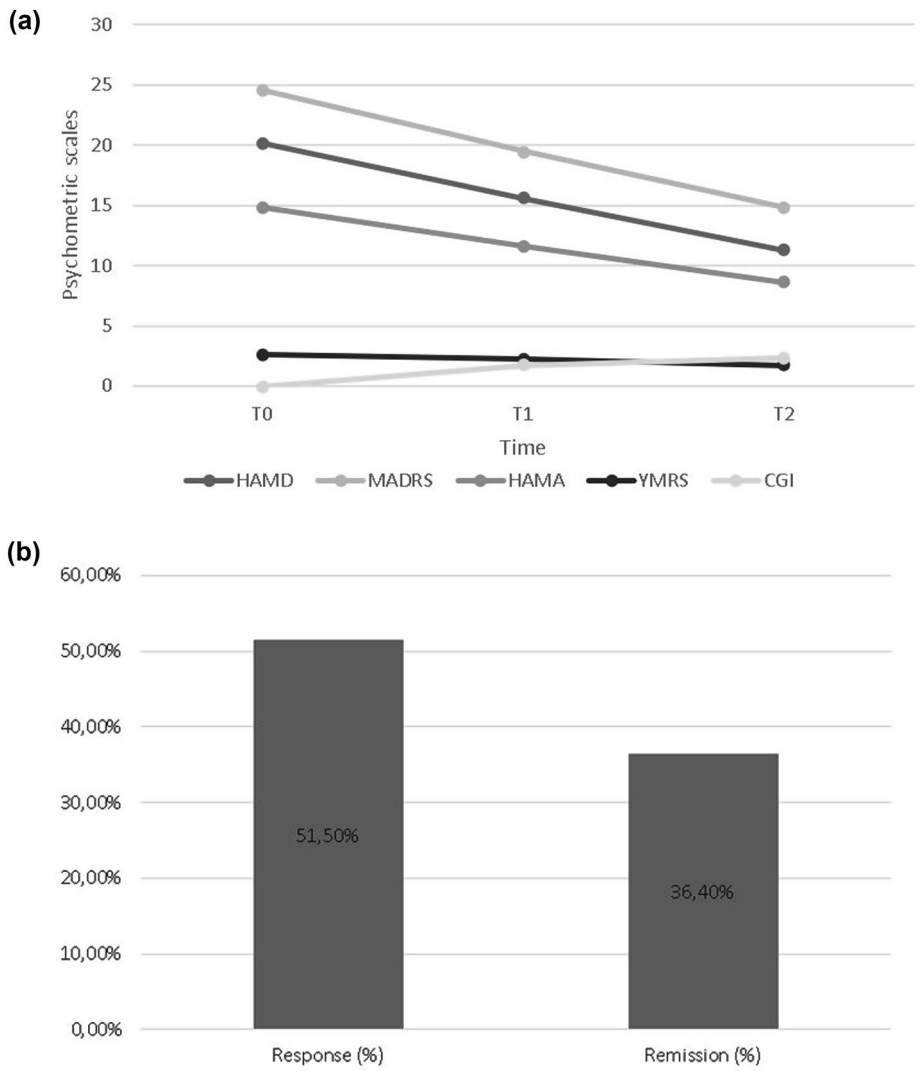


**FIGURE 1** Results of quantitative and qualitative analysis. (a) Psychometric evaluations across time points for the total sample. *Note*: T0, when vortioxetine was started, T1, after 4 weeks, T2, after 3 months; CGI, clinical global impression; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale. (b) Remission and response rates in the total sample. *Note*: Dropouts at T2 were not taken into account for statistical analysis related to remission rates, while dropouts at T1 were excluded for analysis on response rate. Remission percentage is referred to the 42 patients who completed T2 evaluations, while response percentage is referred to the 57 patients who completed at least T1 evaluations

between groups of different dosages in relation to effectiveness, and only a statistically nonsignificant trend of association between increasing dosages of vortioxetine and higher improvements on psychometric scales was observed. Probably, the presence of polycomorbidity and polytherapy in our sample could be the reason of this finding. Indeed, a meta-analysis of studies with vortioxetine (5–20 mg/day) showed a significant dose relationship in the clinical effect, particularly for the overall increasing effect size associated with higher doses (Thase, Mahableshwarkar, Dragheim, Loft, & Vieta, 2016). Such an effect could depend on the higher percentage of occupancy of the serotonin transporter (Areberg, Luntang-Jensen, Søgaard, & Nilausen, 2012). However, a variable efficacy of vortioxetine at lower dosage (5 mg) was supported by different studies in patients with MDD (Alvarez et al., 2012; Baldwin et al., 2012; Henigsberg et al., 2012; Katona et al., 2012), in particular, in case of depressive symptoms associated with mild cognitive impairment (Cumbo, Cumbo, Torregrossa, & Migliore, 2019). In addition, it could be hypothesized that, when other psychotropic drugs, particularly antidepressants, are associated with vortioxetine, like in the majority of our sample, lower dosages might be necessary to show clinical improvements. Furthermore, it could be hypothesized that the nonsignificant trend of efficacy with higher dosages observed could have become statistically significant with a larger sample.

## 4.2 | Tolerability

Overall, two-thirds of recruited patients did not report any side effects, while in the other third, the 72.7% experimented gastrointestinal side effects (mainly nausea, vomit, and diarrhea) and the 22.7%

**TABLE 3** Response and remission rates in the total sample and comparing different dosage subgroups

| | **Total sample** | |
|---|---|---|
| Response | 51.5% ($N = 34/57$) | |
| Remission | 36.4% ($N = 24/42$) | |
| | **Vortioxetine 20 mg** | **Vortioxetine ≤ 10 mg** |
| Response yes | 60.0% ($N = 12$, tot = 20) | 66.7% ($N = 20$, tot = 30) |
| Response no | 40.0% ($N = 8$, tot = 20) | 33.3% ($N = 10$, tot = 30) |
| Remission yes | 58.8% ($N = 10$, tot = 17) | 66.7% ($N = 14$, tot = 21) |
| Remission no | 41.2% ($N = 7$, tot = 17) | 33.3% ($N = 7$, tot = 21) |
| | **Vortioxetine 20 mg** | **Vortioxetine < 20 mg** |
| Response yes | 60.0% ($N = 12$, tot = 20) | 59.5% ($N = 22$, tot = 37) |
| Response no | 40.0% ($N = 8$, tot = 20) | 40.5% ($N = 15$, tot = 37) |
| Remission yes | 58.8% ($N = 10$, tot = 17) | 56.0% ($N = 14$, tot = 25) |
| Remission no | 41.2% ($N = 7$, tot = 17) | 44.0% ($N = 11$, tot = 25) |
| | **Vortioxetine ≥ 15 mg** | **Vortioxetine < 15 mg** |
| Response yes | 53.8% ($N = 14$, tot = 26) | 64.5% ($N = 20$, tot = 31) |
| Response no | 46.2% ($N = 12$, tot = 26) | 35.5% ($N = 11$, tot = 31) |
| Remission yes | 47.6% ($N = 10$, tot = 21) | 66.7% ($N = 14$, tot = 21) |
| Remission no | 52.4% ($N = 11$, tot = 21) | 33.3% ($N = 7$, tot = 21) |
| | **Vortioxetine > 10 mg** | **Vortioxetine ≤ 10 mg** |
| Response yes | 51.9% ($N = 14$, tot = 27) | 66.7% ($N = 20$, tot = 30) |
| Response no | 48.1% ($N = 13$, tot = 27) | 33.3% ($N = 10$, tot = 30) |
| Remission yes | 47.6% ($N = 10$, tot = 21) | 66.7% ($N = 14$, tot = 21) |
| Remission no | 52.4% ($N = 11$, tot = 21) | 33.3% ($N = 7$, tot = 21) |

*Note*: Dropouts at T2 were not taken into account for statistical analysis related to remission rates (percentage referred to 57 patients completing the entire follow-up), while dropouts at T1 were excluded for analysis on response rate (percentage referred to 42 patients completing at least the T1 evaluation).

gastrointestinal ones associated with other side effects (mainly headache and sweating). Indeed, It is well established that vortioxetine's most common side effect is nausea (affecting more than one in 10 people) (EMA, 2014; McIntyre, 2017), generally with mild or moderate severity related to high dosage and usually decreasing or extinguishing in few weeks (De Bartolomeis, Fagiolini, & Maina, 2016). In the same direction, the duration of side effects, in the present study, slightly exceeded 4 weeks (37.17 ± 33.12 days): conversely, the reported severity of side effects was moderate–severe (36.4% moderate and 36.4% severe), and a worse tolerability was not associated with high doses of vortioxetine. Moreover, no weight gain emerged in our sample, in line with other published placebo-controlled trials and open-label extension studies with vortioxetine (Baldwin et al., 2016). This aspect represents an important feature of this drug, for both young and elderly patients, avoiding negative metabolic effects and related reasons of treatment discontinuation (Salagre et al., 2018). Furthermore, vortioxetine showed a favorable profile in terms of sexual side effects in the studied sample: only one patient (4.5%) reported this specific side effect, and we could not exclude that it was related to other concomitant treatment. In other studies, vortioxetine showed a lower rate of sexual dysfunctions compared to other antidepressants, reported in <2% of vortioxetine-treated patients (Baldwin et al., 2016; McIntyre, 2017). Although in the present study no significant differences among vortioxetine dosage groups were observed, in other trials, sexual dysfunction was found to be more frequent with higher doses, but always lower than those of selective serotonin reuptake inhibitors (SSRIs) (Jacobsen, Mahableshwarkar, Chen, Chrones, & Clayton, 2015). Thus, switching treatment with SSRI to vortioxetine showed an important advantage for patients experiencing sexual dysfunction due to SSRIs (Jacobsen et al., 2015). It represents a valuable feature of vortioxetine, as sexual side effects are very common among other antidepressants and often cause reduced adherence to treatment (Serretti & Chiesa, 2009).

## 4.3 | Dropouts

Vortioxetine is one of the most tolerable antidepressants, associated with the lowest rate of dropout (Cipriani et al., 2018). In our sample, approximately one third (36.4%, $N = 24$) dropped out. In particular, most patients dropping out at T1 discontinued for side effects (62.5%, $N = 5$), probably because they could not reach T2 for the impacting side effects; however, considering dropouts at T2, the main reason of discontinuation was the lack of efficacy (37.5%, $N = 6$) and, secondly, the persistence of side effects (25.0%, $N = 4$). The possible explanation could be that subjects who reached T2 without a full response to vortioxetine discontinued for the persistence of depressive symptoms. Our study could not investigate whether a slow titration (i.e., through drops) of vortioxetine could have reduced the rate of dropouts, due to side effects, and ultimately increased the rate of patients completing the entire follow-up.

## 4.4 | Limitations

In the present study, some limitations should be taken into account in the interpretation of the aforementioned findings. First, the limited recruited study sample and then the following methodological limitations should be considered. For example, referring to collected sociodemographic and clinical variables, the presence of recall bias cannot be excluded, particularly for patients with most remote onset, as well as the retrospective collection bias from previous medical charts. Moreover, our sample showed different illness severities, and most of the patients had previously been exposed to other antidepressants. Furthermore, the presence of polycomorbidities (both medical and psychiatric), concomitant treatments in the majority of

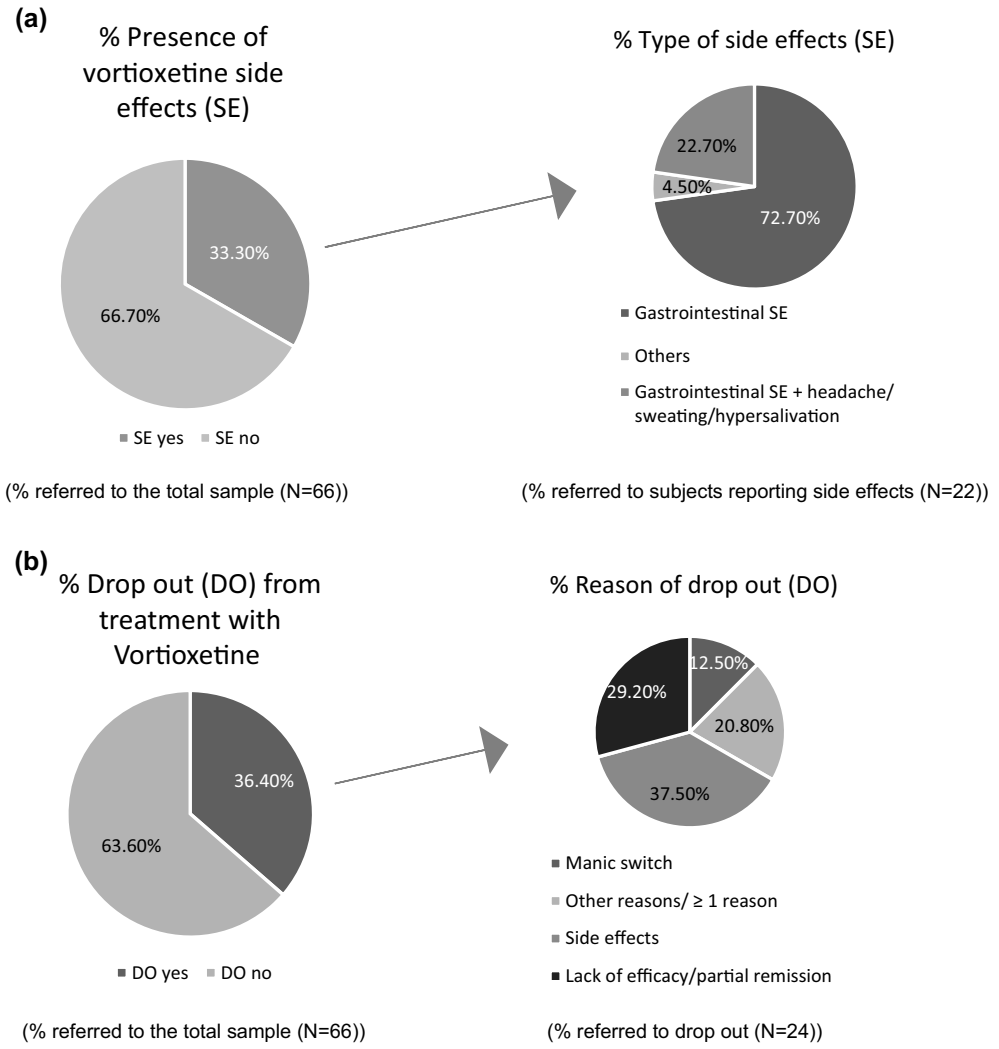


**FIGURE 2** (a) Side effects (SEs) rate and type of SEs. (b) Dropout (DO) rate and reasons of DO

the sample and different dosages of vortioxetine and/or different regimens in terms of unique versus multiple daily administration and finally a different titration process, might have ultimately conditioned the vortioxetine efficacy as well as the onset of side effects and dropout rates. Lastly, the present results have to be confirmed considering a comparison group treated with placebo or a different active medication.

## 5 | CONCLUSION

In conclusion, the present report confirms the effectiveness of vortioxetine over affective symptoms, along with a favorable tolerability profile and low dropout rates, independently from daily dosages, in a sample of patients with polycomorbidities and polytherapy.

In order to assess whether higher dosages of vortioxetine can determine a larger quantitative and qualitative responses, maintaining a favorable tolerability profile, larger samples, and further studies are warranted in the real world, including patients with polycomorbidity, polytherapy, long duration of illness, and previous exposure to other antidepressants.

### ACKNOWLEDGEMENTS

We acknowledge the advice from all contributors of the present naturalistic study.

### CONFLICT OF INTERESTS

Vera De Carlo, Matteo Vismara, Benedetta Grancini, and Anna Colombo report no financial relationships with commercial interests. Benatti Beatrice has received a consultant fee from Lundbeck. Bosi Monica Francesca has received a speaker fee from Lundbeck. Viganò Caterina Adele has received speaker fees from Lundbeck and Angelini. Prof. Dell'Osso has received lecture honoraria from Angelini, Jansen, Lundbeck, Livanova, Arcapharma, and Neuraxpharm.

### AUTHOR CONTRIBUTIONS

All authors contributed to and have approved the final manuscript.

## ORCID

*Vera De Carlo* https://orcid.org/0000-0002-0395-0402


## REFERENCES


Alam, M. Y., Jacobsen, P. L., Chen, Y., Serenko, M., & Mahableshwarkar, A. R. (2014). Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: Results of an open-label, flexible-dose, 52-week extension study. *International Clinical Psychopharmacology*, *29*(1), 36–44. https://doi.org/10.1097/YIC.0000000000000010

Alvarez, E., Perez, V., Dragheim, M., Loft, H., & Artigas, F. (2012). A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *The International Journal of Neuropsychopharmacology*, *15*(5), 589–600. https://doi.org/10.1017/S1461145711001027

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Association.

Areberg, J., Luntang-Jensen, M., Søgaard, B., & Nilausen, D. Ø. (2012). Occupancy of the serotonin transporter after administration of Lu AA21004 and its relation to plasma concentration in healthy subjects. *Basic & Clinical Pharmacology & Toxicology*, *110*(4), 401–404. https://doi.org/10.1111/j.1742-7843.2011.00810.x

Atique-Ur-Rehman, H., & Neill, J. C. (2019). Cognitive dysfunction in major depression: From assessment to novel therapies. *Pharmacology and Therapeutics*, *202*, 53–71. https://doi.org/10.1016/j.pharmthera.2019.05.013

Baldwin, D. S., Chrones, L., Florea, I., Nielsen, R., Nomikos, G. G., Palo, W., & Reines, E. (2016). The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. *Journal of Psychopharmacology (Oxford, England)*, *30*(3), 242–252. https://doi.org/10.1177/0269881116628440

Baldwin, D. S., Florea, I., Jacobsen, P. L., Zhong, W., & Nomikos, G. G. (2016). A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms. *Journal of Affective Disorders*, *206*, 140–150. https://doi.org/10.1016/j.jad.2016.07.015

Baldwin, D. S., Hansen, T., & Florea, I. (2012). Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Current Medical Research and Opinion*, *28*(10), 1717–1724. https://doi.org/10.1185/03007995.2012.725035

Baldwin, D. S., Loft, H., & Dragheim, M. (2012). A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *22*(7), 482–491. https://doi.org/10.1016/j.euroneuro.2011.11.008

Bang-Andersen, B., Ruhland, T., Jørgensen, M., Smith, G., Frederiksen, K., Jensen, K. G., … Stensbøl, T. B. (2011). Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): A novel multimodal compound for the treatment of major depressive disorder. *Journal of Medicinal Chemistry*, *54*(9), 3206–3221. https://doi.org/10.1021/jm101459g

Bauer, M., Pfennig, A., Severus, E., Whybrow, P. C., Angst, J., Möller, H.-J., & World Federation of Societies of Biological Psychiatry. Task Force on Unipolar Depressive Disorders. (2013). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *14*(5), 334–385. https://doi.org/10.3109/15622975.2013.804195

Berhan, A., & Barker, A. (2014). Vortioxetine in the treatment of adult patients with major depressive disorder: A meta-analysis of randomized double-blind controlled trials. *BMC Psychiatry*, *14*, 276. https://doi.org/10.1186/s12888-014-0276-x

Boulenger, J.-P., Loft, H., & Olsen, C. K. (2014). Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: A randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *International Clinical Psychopharmacology*, *29*(3), 138–149. https://doi.org/10.1097/YIC.0000000000000018

Charara, R., Forouzanfar, M., Naghavi, M., Moradi-Lakeh, M., Afshin, A., Vos, T., … Mokdad, A. H. (2017). The burden of mental disorders in the Eastern Mediterranean region, 1990-2013. *PloS One*, *12*(1), e0169575. https://doi.org/10.1371/journal.pone.0169575

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., … Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet*, *391*(10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Corruble, E., & Guelfi, J. D. (2000). Pain complaints in depressed inpatients. *Psychopathology*, *33*(6), 307–309. https://doi.org/10.1159/000029163

Cumbo, E., Cumbo, S., Torregrossa, S., & Migliore, D. (2019). Treatment effects of vortioxetine on cognitive functions in mild Alzheimer's disease patients with depressive symptoms: A 12 month, open-label, observational study. *The Journal of Prevention of Alzheimer's Disease*, *6*(3), 192–197. https://doi.org/10.14283/jpad.2019.24

De Bartolomeis, A., Fagiolini, A., & Maina, G. (2016). Vortioxetine in the treatment of major depression. *Rivista di Psichiatria*, *51*(6), 215–230. https://doi.org/10.1708/2596.26720

De Carlo, V., Calati, R., & Serretti, A. (2016). Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Research*, *240*, 421–430. https://doi.org/10.1016/j.psychres.2016.04.034

Dell'Osso, B., Cremaschi, L., Arici, C., Altamura, A. C., Hooshmand, F., Do, D., … Ketter, T. A. (2020). Differential core pharmacotherapy in bipolar I versus bipolar II disorder and European versus American patients not in a syndromal episode. *International Clinical Psychopharmacology*, *35*(1), 8–18. https://doi.org/10.1097/YIC.0000000000000282

European Medicines Agency (EMA). (2014). *EPAR brintellix - product information. Annex I. Summary of product characteristics*. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002717/WC500159449.pdf

First, M., Williams, J., Benjamin, L., & Spitzer, R. (2015). *User's guide for the SCID-5-PD (structured clinical interview for DSM-5 personality disorder)*. Arlington, VA: American Psychiatric Association.

First, M., Williams, J., Karg, R., & Spitzer, R. (2016). *Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association.

Food and Drug Administration (FDA). (2013). *Brintellix TM (vortioxetine) tablets for oral use. Full prescribing information*. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf

Galimberti, C., Bosi, M. F., Caricasole, V., Zanello, R., Dell'Osso, B., & Viganò, C. A. (2019). Using network analysis to explore cognitive domains in patients with unipolar versus bipolar depression: A prospective naturalistic study. *CNS Spectrums*, *25*(3), 380–391. https://doi.org/10.1017/S1092852919000968

Grunze, H., Vieta, E., Goodwin, G. M., Bowden, C., Licht, R. W., Möller, H.-J., … WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. (2013). The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2012 on the long-term treatment of bipolar disorder. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *14*(3), 154–219. https://doi.org/10.3109/15622975.2013.770551

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, *32*(1), 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology*, *6*(4), 278–296. https://doi.org/10.1111/j.2044-8260.1967.tb00530.x

Henigsberg, N., Mahableshwarkar, A. R., Jacobsen, P., Chen, Y., & Thase, M. E. (2012). A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *The Journal of Clinical Psychiatry*, *73*(7), 953–959. https://doi.org/10.4088/JCP.11m07470

Hughes, S., Lacasse, J., Fuller, R. R., & Spaulding-Givens, J. (2017). Adverse effects and treatment satisfaction among online users of four antidepressants. *Psychiatry Research*, *255*, 78–86. https://doi.org/10.1016/j.psychres.2017.05.021

Jacobsen, P. L., Harper, L., Chrones, L., Chan, S., & Mahableshwarkar, A. R. (2015). Safety and tolerability of vortioxetine (15 and 20 mg) in patients with major depressive disorder: Results of an open-label, flexible-dose, 52-week extension study. *International Clinical Psychopharmacology*, *30*(5), 255–264. https://doi.org/10.1097/YIC.0000000000000081

Jacobsen, P. L., Mahableshwarkar, A. R., Chen, Y., Chrones, L., & Clayton, A. H. (2015). Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *The Journal of Sexual Medicine*, *12*(10), 2036–2048. https://doi.org/10.1111/jsm.12980

Jacobsen, P. L., Mahableshwarkar, A. R., Serenko, M., Chan, S., & Trivedi, M. H. (2015). A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *The Journal of Clinical Psychiatry*, *76*(5), 575–582. https://doi.org/10.4088/JCP.14m09335

Jain, R., Mahableshwarkar, A. R., Jacobsen, P. L., Chen, Y., & Thase, M. E. (2013). A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *The International Journal of Neuropsychopharmacology*, *16*(2), 313–321. https://doi.org/10.1017/S1461145712000727

Katona, C., Hansen, T., & Olsen, C. K. (2012). A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *International Clinical Psychopharmacology*, *27*(4), 215–223. https://doi.org/10.1097/YIC.0b013e3283542457

Lochner, C., Fineberg, N. A., Zohar, J., Van Ameringen, M., Juven-Wetzler, A., Altamura, A. C., … Stein, D. J. (2014). Comorbidity in obsessive-compulsive disorder (OCD): A report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). *Comprehensive Psychiatry*, *55*(7), 1513–1519. https://doi.org/10.1016/j.comppsych.2014.05.020

Mahableshwarkar, A. R., Jacobsen, P. L., & Chen, Y. (2013). A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Current Medical Research and Opinion*, *29*(3), 217–226. https://doi.org/10.1185/03007995.2012.761600

McIntyre, R. S. (2017). The role of new antidepressants in clinical practice in Canada: A brief review of vortioxetine, levomilnacipran ER, and vilazodone. *Neuropsychiatric Disease and Treatment*, *13*, 2913–2919. https://doi.org/10.2147/NDT.S150589

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, *134*(4), 382–389. https://doi.org/10.1192/bjp.134.4.382

Nomikos, G. G., Tomori, D., Zhong, W., Affinito, J., & Palo, W. (2017). Efficacy, safety, and tolerability of vortioxetine for the treatment of major depressive disorder in patients aged 55 years or older. *CNS Spectrums*, *22*(4), 348–362. https://doi.org/10.1017/S1092852916000626

Pae, C. U., Wang, S. M., Han, C., Lee, S. J., Patkar, A. A., Masand, P. S., & Serretti, A. (2015). Vortioxetine: A meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. *Journal of Psychiatry and Neuroscience*, *40*(3), 174–186. https://doi.org/10.1503/jpn.140120

Papakostas, G. I. (2014). Cognitive symptoms in patients with major depressive disorder and their implications for clinical practice. *Journal of Clinical Psychiatry*, *75*(1), 8–14. https://doi.org/10.4088/JCP.13r08710

Papakostas, G. I., Nielsen, R. Z., Dragheim, M., & Tonnoir, B. (2018). Efficacy and tolerability of vortioxetine versus agomelatine, categorized by previous treatment, in patients with major depressive disorder switched after an inadequate response. *Journal of Psychiatric Research*, *101*, 72–79. https://doi.org/10.1016/j.jpsychires.2018.02.017

Pehrson, A. L., Leiser, S. C., Gulinello, M., Dale, E., Li, Y., Waller, J. A., & Sanchez, C. (2015). Treatment of cognitive dysfunction in major depressive disorder--A review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetine. *European Journal of Pharmacology*, *753*, 19–31. https://doi.org/10.1016/j.ejphar.2014.07.044

Rizvi, S. J., & Kennedy, S. H. (2011). The keys to improving depression outcomes. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *21*(Suppl. 4), S694–S702. https://doi.org/10.1016/j.euroneuro.2011.07.002

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Salagre, E., Grande, I., Solé, B., Sanchez-Moreno, J., & Vieta, E. (2018). Vortioxetine: A new alternative for the treatment of major depressive disorder. *Revista de Psiquiatria y Salud Mental*, *11*(1), 48–59. https://doi.org/10.1016/j.rpsm.2017.06.006

Serretti, A., & Chiesa, A. (2009). Treatment-emergent sexual dysfunction related to antidepressants: A meta-analysis. *Journal of Clinical Psychopharmacology*, *29*(3), 259–266. https://doi.org/10.1097/JCP.0b013e3181a5233f

Thase, M. E., Mahableshwarkar, A. R., Dragheim, M., Loft, H., & Vieta, E. (2016). A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults. *European Neuropsychopharmacology*, *26*(6), 979–993.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry*, *133*(11), 429–435. https://doi.org/10.1192/bjp.133.5.429

Zheng, Y., Severino, F., Hui, L., Wu, H., Wang, J., & Zhang, T. (2019). Comorbidity of DSM-IV personality disorder in major depressive disorder among psychiatric outpatients in China: A further analysis of an Epidemiologic Survey in a clinical population. *Frontiers in Psychiatry*, *10*, 833. https://doi.org/10.3389/fpsyt.2019.00833

**How to cite this article:** De Carlo V, Vismara M, Grancini B, et al. Effectiveness, tolerability, and dropout rates of vortioxetine in comorbid depression: A naturalistic study. *Hum Psychopharmacol Clin Exp*. 2020;e2750. https://doi.org/10.1002/hup.2750