Original Research

Effectiveness and Tolerability of Supratherapeutic Dosing of Vortioxetine in Patients With Treatment-Resistant Depression

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ABSTRACT

Objective: To evaluate the effectiveness and tolerability of vortioxetine at supratherapeutic dosages in patients with treatment-resistant depression.

Methods: A retrospective observational naturalistic study was conducted in 56 depressed patients resistant to standard care treatment from September 2020 to April 2021. Effectiveness of the vortioxetine treatments was evaluated through Clinical Global Impressions (CGI) score, comparing CGI values at the beginning (T_0) of the vortioxetine treatment with CGI values at the earliest of these 2 time points (T_1): (1) 8 weeks of treatment with supratherapeutic dosages and (2) day of vortioxetine discontinuation or daily dosage reduction to ≤ 20 mg due to side effects. The tolerability and safe of vortioxetine were also monitored.

Results: Fifty-six patients (32 females and 24 males, mean ± SD age of 51.1 ± 9.3 years) were included in the study. Thirty-seven patients received vortioxetine 30 mg/d, while 19 patients were treated with a 40-mg/d dosage. CGI scores significantly decreased ($P < .001$) in patients treated with 30 mg/d and 40 mg/d, respectively. No severe side effects were reported. Weight gain and nausea were the most common reported side effects. Nausea and limited efficacy were recorded as the most frequent reasons for vortioxetine dose reduction. None of the patients required vortioxetine discontinuation.

Conclusions: Supratherapeutic doses of vortioxetine were relatively well-tolerated and effective in patients with treatment-resistant depression.

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A relatively high number of patients do not respond to multiple courses of antidepressant treatments.[1–3] In the STAR*D trials, one-third of patients never remitted, even after 4 consecutive treatments.[4,5]

Optimization of current medication dose, switching to another antidepressant, add-on treatments (eg, lithium, atypical antipsychotics, esketamine, or thyroid hormones), and brain stimulation techniques (eg, electroconvulsive therapy, repetitive transcranial magnetic stimulation, vagal nerve stimulation, or deep brain stimulation) are among the most used strategies to treat resistant depression.[6–8]

Increasing the antidepressant dose up to the standard tolerated maximal dose is considered an efficiency strategy.[9,10] Patients showing good tolerability and partial response or patients who have previously required unusually high medication doses may benefit from dose optimization up to supratherapeutic dosage (eg, sertraline 250 mg to 350 mg).[8]

Vortioxetine is a multimodal antidepressant approved in 2013 by the US Food and Drug Administration and the European Medicines Agency for the treatment of major depressive disorder (MDD) in adults at an oral dosage of 5–20 mg/d. In Italy, it has been available since May 2016.[11]

Vortioxetine has a unique and multimodal mechanism of action that combines inhibition of the serotonin transporter with modulation of serotonin (5-hydroxytryptamine [5-HT]) receptor activity.[12] Furthermore, it acts as a 5-HT1B receptor partial agonist and 5-HT3, 5-HT7, and 5-HT1D receptor antagonist and modulates neurotransmission in multiple systems.[13] It has been hypothesized that vortioxetine also has procognitive actions.[14] Contrary to selective serotonin reuptake inhibitors, it blocks self-regulating systems (5-HT1B, 5-HT1D, 5-HT7).[14]

Vortioxetine pharmacokinetics are linear and not affected by food intake. Plasma concentration increases proportionally with a single dose between 5 and 20 mg/d, reaching the peak within 7 to 11 hours (T_{max}).[15] Its absolute bioavailability is 75% after oral administration with a large volume of distribution (approximately 2,600 L), which results in a long half-life of approximately 66 hours.

Vortioxetine is extensively distributed into the extravascular compartment and is metabolized extensively by the liver through oxidation via several cytochrome P450 isoenzymes and subsequent glucuronic conjugation via uridine diphosphate-glucuronosyltransferase.[13,15] The major metabolite Lu AA3443 is pharmacologically inactive and mainly excreted through the kidneys.[16] The minor pharmacologically active metabolite is not expected to cross the blood-brain barrier.[13]

This study aimed to evaluate the efficacy and tolerability of supratherapeutic doses of vortioxetine in patients with treatment-resistant depression.

Clinical Points

- Only a few treatments are approved for treatment-resistant depression.
- When the approved treatments for treatment-resistant depression are not available or feasible, vortioxetine at supratherapeutic doses may be an option.
- In patients with treatment-resistant depression, vortioxetine at supratherapeutic (20–40 mg) doses has shown a favorable balance between risks and benefits.

Table 1. Patient Characteristics[a]

Characteristic	Total Sample (N = 56)
Sex	
Male	24 (42.9)
Female	32 (57.1)
Age, mean (SD), range, y	51.1 (9.3) (27–71)
Vortioxetine dose	
30 mg	37 (66.1)
40 mg	19 (33.9)
Concomitant medications	38 (67.9)
Antipsychotic	22 (39.3)
Benzodiazepine	8 (14.3)
Antidepressant	16 (28.6)
Mood stabilizer	26 (46.4)

[a]Values are presented as n (%) unless otherwise specified.

METHODS

This retrospective observational naturalistic study aimed to assess the efficacy and tolerability of supratherapeutic doses of vortioxetine in patients with MDD who experienced an episode of treatment-resistant depression. The study was approved by the University of Siena and Area Vasta–South-East Institutional Review Board Ethics Committee (protocol no. 17617, approval date June 15, 2020). The study was conducted from September 2020 to April 2021.

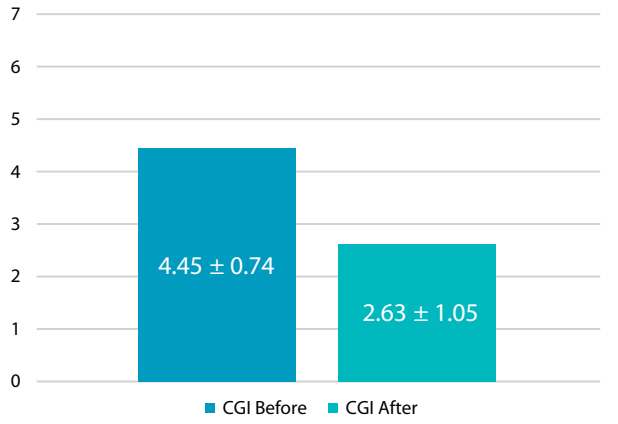
Patients were enrolled using the following criteria: (1) diagnosis of MDD according to the *DSM-5*; (2) diagnosis of treatment-resistant depression, defined as failure to respond to 2 or more different oral antidepressants given at an adequate dose and for a sufficiently long period; (3) a Montgomery-Asberg Depression Rating Scale[17] score ≥ 20; and (4) treated with vortioxetine 30 mg/d or 40 mg/d because of treatment-resistant depression. Patients with concurrent medications/treatments and patients with bipolar traits (ie, subthreshold bipolar disorder) were also included.

All patients gave informed consent to be treated with supratherapeutic doses of vortioxetine. Patients were treated either at the Psychiatry Department of the University of Siena Medical Center or the Crotone Mental Health Center outpatient unit in Italy. Slow titration of vortioxetine was applied for all patients.

The Clinical Global Impressions (CGI)[18] score was measured at baseline ([T_0]; the first day in which the dose of vortioxetine was increased above the maximum recommended dose of 20 mg/d) and after 8 weeks of treatment with supratherapeutic doses (T_1). If a dose reduction due to side effects was decided before the end of the 8 weeks of observation, the CGI-Severity (CGI-S) score endpoint (T_1) was the CGI of the day when vortioxetine was discontinued or reduced to a daily dose of ≤ 20 mg.

Descriptive statistical analyses were presented as mean ± SD for quantitative variables and frequencies and percentages for qualitative variables. The effectiveness of treatment, ie, changes in CGI-S scores after the treatment with vortioxetine supratherapeutic doses, was assessed through Wilcoxon matched-pairs signed rank test. Statistical significance was set at 5% ($P < .05$).

Figure 1. CGI Scores Before and After Treatment With Vortioxetine[a]



[a]Values are presented as mean ± SD.

Table 2. Weight Gain, Nausea, and Reduced Efficacy

Variable	Total Sample (N = 56)[a]
Weight gain[b]	
No	50 (89.3)
Yes	6 (10.7)
Nausea	
No	34 (60.7)
Yes	22 (39.3)
Efficacy	43 (76.8)
Reduced efficacy	13 (23.2)

[a]Values are presented as n (%).
[b]Weight gain was defined as an increase > 5% from baseline.

RESULTS

Fifty-six patients (32 females and 24 males) were included in the study. The mean ± SD age was 51.1 ± 9.3 years. Thirty-seven patients received vortioxetine 30 mg/d, and the remaining 19 patients were treated with vortioxetine 40 mg/d. Thirty-eight patients were receiving concomitant medications when vortioxetine was administered. Patient characteristics and concomitant medications are reported in Table 1.

Overall, CGI scores significantly improved from T_0 to T_1 (CGI T_0: 4.45 ± 0.74, CGI T_1: 2.63 ± 1.05, $P < .001$) (Figure 1). No serious adverse events emerged during the observation period. Weight gain (defined as weight increased by more than 5% from baseline) and nausea were observed in 6 (10.7%) and 22 (39.3%) of the patients treated with vortioxetine 30 and 40 mg, respectively (Table 2). No symptoms or signs of serotonin

Table 3. Vortioxetine Maintenance Dose Reduction

Dose	Total Sample (N = 56)[a]
No reduction	21 (37.5)
Reduction because of nausea	22 (39.3)
Reduction because of reduced efficacy	13 (23.2)

[a]Values are presented as n (%).

syndrome were observed or recorded. A dose reduction to a daily dose of ≤ 20 mg was made before 8 weeks of treatment for 35 patients because of nausea (22 patients) or lack of improvement (13 patients) (Table 3).

DISCUSSION

Many studies[19–21] have demonstrated the efficacy of vortioxetine in the treatment of depression with a dosage between 5 and 20 mg/d. Our study aimed to evaluate the efficacy and tolerability of vortioxetine when used at supratherapeutic doses in patients with resistant depression. After 8 weeks of treatment, patients showed a significant improvement of CGI score ($P < .0001$) with no severe side effects reported. Consistent with what has been observed with therapeutic doses of 5–20 mg/d,[22] no worsening of suicidal ideation or suicidal behaviors was recorded in our study.

Contrary to previous studies with vortioxetine at doses of 10 or 20 mg,[19,23–25] weight gain was observed more frequently. However, the higher prevalence of weight gain could also be due to the concomitant medications, which included mood stabilizers (46% of study subjects) and antipsychotics (39% of study subjects). In previous reports, no major side effects were reported for accidental or intentional intake of vortioxetine dosages ranging from 40 mg to 250 mg daily.[26]

The main limitations of our study include the small sample size, the retrospective design, the lack of randomization, the lack of a placebo arm, and a Berkson bias due to the likelihood that the study selected patients with more severe illness than the average patient with treatment-resistant depression. Hence, our results should be considered very preliminary. However, we hope that this study will prompt more research to test the efficacy and tolerability of vortioxetine at supratherapeutic doses. This study suggests the safety and efficacy of supratherapeutic doses of vortioxetine to treat resistant depression.

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