

BRIEF COMMUNICATION

Adjunctive vortioxetine for SSRI-resistant major depressive disorder: a “real-world” chart review study

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are the cornerstone of treatment of major depressive disorder (MDD). However, non-response is common, often necessitating combination strategies. The present study assessed the efficacy of vortioxetine as an add-on therapy in patients with SSRI-resistant MDD.

Methods: The charts of 36 adult outpatients with DSM-IV-TR MDD who had not achieved a response after at least 8 weeks of treatment with an SSRI were reviewed retrospectively. Subjects were treated with vortioxetine (5-20 mg/day) for 8 weeks added to the current SSRI. The main outcome measures were change from baseline in total Hamilton Scale for Depression (HAM-D) score and the rate of response (a 50% or greater reduction in HAM-D score and a Clinical Global Impression - Improvement module [CGI-I] score of 1 or 2 at endpoint). HAM-D scores ≤ 7 were considered as remission. Additional outcome measures included the Snaith-Hamilton Pleasure Scale (SHAPS) and the Scale for Suicide Ideation (SSI).

Results: 32 patients completed the 8 weeks of treatment. At 8 weeks, a significant reduction in HAM-D score was observed ($p \leq 0.001$), with response obtained by 41.7% and remission by 33.3% of patients. Significant reductions in SHAPS and SSI were also observed ($p \leq 0.001$ for both scales).

Conclusions: Adjunctive vortioxetine may be useful and well-tolerated in stage I treatment-resistant depression. However, the limitations of this study (such as small sample size, absence of randomization and control group, retrospective design, etc.) must be considered.

Keywords: Vortioxetine; SSRI-resistant major depressive disorder; chart study; augmentation; retrospective; real world

Introduction

Major depressive disorder (MDD) is a chronic, severe, disabling psychiatric disorder that has a substantial impact on public health and human functioning.^{1,2} Although antidepressants are useful in most cases, it is well known that

a substantial number of subjects with MDD do not achieve response or remission with first-line antidepressant therapy, as demonstrated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, in which less than 30% of patients achieved remission with first-line citalopram.³⁻⁵ This condition is known as treatment-resistant

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depression (TRD).⁶ In the classification proposed by Thase & Schwartz,⁷ stage I TRD is defined by the persistence of significant depressive symptoms despite at least one adequate trial with one major class of antidepressant; stage II is stage I resistance plus failure of a proper trial with an antidepressant drug in a different class from that used in stage I; and stage III is stage II resistance plus failure of a proper trial with a tricyclic antidepressant. Several pharmacological augmentation strategies have been evaluated in the treatment of TRD, including antidepressants (such as monoamine oxidase inhibitors, agomelatine, bupropion, etc.), mood stabilizers (lithium, lamotrigine, etc.), antipsychotics (quetiapine, aripiprazole, amisulpride), ketamine, pindolol, and other drugs.⁸⁻¹¹ However, the search for further options is welcome, as current augmentation strategies are still ineffective in many cases.

Vortioxetine is a recently introduced multimodal antidepressant that inhibits the serotonin transporter (SERT) and antagonizes several serotonin receptors (5-HT₃, 5-HT₇, and 5-HT_{1D}).¹² It also acts as a partial agonist on 5-HT_{1B} and as a full agonist on 5-HT_{1A} receptors.¹³ Vortioxetine binds with high affinity to the SERT (K_i = 1.6 nM). Its presumed mechanism of action is enhancement of serotonin in the central nervous system through reuptake inhibition, meaning it can be used together with selective serotonin reuptake inhibitors (SSRIs) or instead of them in clinical practice.¹² The efficacy of vortioxetine in the treatment of MDD is well demonstrated.¹⁴ A systematic review and network meta-analysis showed that, in head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants.¹⁵ Citrome pointed out that vortioxetine had similar efficacy to duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, and was 5.1 times more likely to be associated with response than discontinuation because of an adverse event when compared to placebo.¹⁶

However, to date, the combination of vortioxetine with standard SSRIs in stage I TRD has not yet been investigated. In this context, this “real-world” retrospective study was designed to evaluate the efficacy and tolerability of vortioxetine augmentation in subjects with stage I TRD in everyday clinical practice.

Methods

The charts of 44 consecutive adult outpatients (26 men, 18 women) with a DSM-IV-TR diagnosis of MDD, obtained from mental health facilities in Italy, were reviewed retrospectively between January 2018 and February 2019. Psychiatrists with at least 5 years of clinical experience made the diagnoses of MDD. The inclusion criteria were: 1) major depressive episode (MDE) resistant to one adequate SSRI treatment (full therapeutic dose for at least 6 consecutive weeks), based on clinician judgment; and 2) a 17-Item Hamilton Depression Rating Scale (HAM-D)¹⁷ score \geq 18.

The exclusion criteria were presence of another axis-I disorder (including anxiety and somatization disorders), pregnancy, breastfeeding, or childbearing potential; patients

who met DSM-IV-TR criteria for abuse or dependence of any drug, including alcohol; and subjects judged by colleagues to be unsuitable for inclusion. Several enrolled patients took low dosages of benzodiazepines (BDZs) in the morning or bedtime for almost 3 months. Subjects under treatment with other medications (including antipsychotics) were excluded.

Six subjects were excluded as they were taking antipsychotics or mood stabilizers, and two were excluded due to comorbid alcohol and cannabis dependence. Thus, 36 subjects (22 men, 14 women) were included in the final analysis. Eight subjects had MDD with melancholic features, whereas three had MDD with atypical features. The SSRIs prior to switch were citalopram (n=5, mean dosage = 40 mg/d); escitalopram (n=14, mean dosage = 23.9 mg/day, range 20-30 mg/day); paroxetine (n=3, mean dosage = 53.3 mg/day, range 40-60 mg/day); and sertraline (n=14, mean dosage = 180.4 mg/day, range 150-250 mg/day).

The primary outcome measure was the HAM-D total score. The Clinical Global Impression - Improvement module (CGI-I) was rated at the endpoint. Assessments were carried out at the baseline visit and every 4 weeks of active treatment until the 8-week endpoint. Additional evaluations included the Snaith-Hamilton Pleasure Scale (SHAPS) to assess anhedonia¹⁸ and the Scale for Suicidal Ideation (SSI).¹⁹ Both scales were available only before the addition of vortioxetine and at 8 weeks of treatment.

Vortioxetine dosage was flexible, based on the psychiatrist's judgment while following the dosing recommendations given in the product information (up to 20 mg/day). The charts of enrolled patients were chosen on this basis. Subjects with a 50% or greater decrease in HAM-D total score and a CGI-I score of 1 or 2 at 8 weeks were classified as responders; remission was defined as a HAM-D overall score of \leq 7.

Any incident adverse events were evaluated through chart review at every follow-up visit and at the end of the 8-week observation period.

Statistical analysis

All demographic and clinical variables in the present study were checked for deviation from the Gaussian distribution using the Kolmogorov-Smirnov test. An intention-to-treat analysis (ITT) was conducted, with the last available evaluation carried forward as an endpoint (last observation carried forward, LOCF). Descriptive statistics and percentages were calculated for demographic variables and all available scales. A repeated-measures analysis of variance (ANOVA) with Tukey's post-hoc test, based on the studentized range distribution, was conducted to evaluate HAM-D scores, whereas Student's *t*-test was used to compare HAM-D, SHAPS, and SSI scores between baseline and endpoint. In all evaluations, statistical significance was accepted at $p = 0.05$.

Ethics statement

The local ethics committee reviewed the study design, and all subjects provided written consent.

Table 1 Demographic and clinical data of study participants (n=36)

Parameter	Baseline	8 weeks (LOCF)	Reduction from baseline (%)	Statistics
Gender				
Male, n (%)	14 (38.9%)	-	-	-
Female, n (%)	22 (61.1%)	-	-	-
Age, years (mean \pm SD)	31.1 \pm 5.8	-	-	-
Current episode duration, weeks (mean \pm SD)	20.7 \pm 6.7	-	-	-
Family history of MD: yes, n (%)	14 (38.9)	-	-	-
Prior hospitalization: yes, n (%)	12 (33.3%)	-	-	-
Prior suicide attempt: yes, n (%)	9 (25%)	-	-	-
Episodes, n (%)				
1	14 (38.9)	-	-	-
2	13 (36.1)	-	-	-
3+	9 (25)	-	-	-
HAM-D total score (mean \pm SD)	31.8 \pm 3.5	12.2 \pm 7.2	61.8	F = 232.4, df = 4, p \leq 0.001
SHAPS total score (mean \pm SD)	7.3 \pm 2.2	3.9 \pm 3.0	50.5	t = 10.0, df=35, p \leq 0.001
SSI total score (mean \pm SD)	13.6 \pm 4.4	5.4 \pm 2.9	55.7	t = 9.1, df=35, p \leq 0.001

HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward; MD = major depression; SHAPS = Snaith-Hamilton Pleasure Scale; SSI = Scale for Suicidal Ideation; SD = standard deviation.

Results

Thirty-two patients completed the 8 weeks of treatment (Table 1). Two patients dropped out due to adverse effects (nausea), one decided to stop treatment due to reported sexual dysfunction, and another one was lost due to relocation, but all were included in the LOCF analysis. The mean vortioxetine dose was 16.4 mg/day (range 5-20 mg/day).

The progression of HAM-D scores over time is shown in Figure 1. The mean (SD) HAM-D score at baseline was 31.8 \pm 3.5, and reduced to 12.2 \pm 7.2 (LOCF) at week 8. The repeated measures ANOVA showed a significant decrease in scores over time (F = 232.4, df = 4, p \leq 0.001, LOCF) with a mean reduction between baseline and endpoint of 19.6 (61.8%). The posthoc test showed that changes from baseline were statistically significant by week 4 (Tukey's q = 14.8, p \leq 0.001). No significant differences in LOCF analyses of HAM-D scores between subjects with one, two and 3 or more episodes were found (respectively 11.1 \pm 6.2, 12.5 \pm 6.2 and 13.3 \pm 10.3).

Based on LOCF analysis, at the end of the trial, a 50% or greater decrease in HAM-D scores from baseline and a score of 1 or 2 on the CGI-I was obtained in 15 patients (41.7%; eight women, five men). Sixteen patients (44.4%; 11 women, five men) had a < 50% reduction in HAM-D scores and were considered non-responders. All patients who dropped out were classified as non-responders. For the LOCF data set, 12 patients (33.3%; eight women, five men) achieved remission (HAM-D score \leq 7 at endpoint). No differences in response/remission were found between subjects with melancholic or atypical MDD, nor between subjects with one episode (nine responders and four remitters), two episodes (six responders and four remitters), and three or more episodes (five responders and four remitters).

The positive effect of vortioxetine augmentation on HAM-D scores was also corroborated by the results of the other efficacy rating scales (Table 1). Significant changes

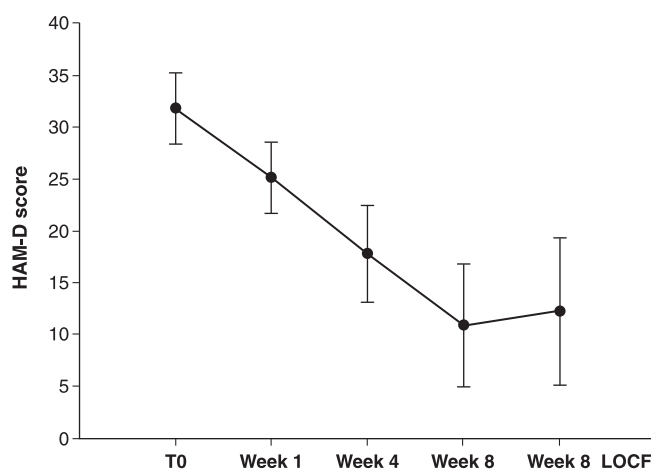


Figure 1 Symptom improvement during the 8-week observation period. Hamilton Rating Scale for Depression (HAM-D) total scores, mean \pm standard deviation (SD) from baseline (T0) to endpoint (week 8); p \leq 0.001, last observation carried forward (LOCF).

from baseline were observed on the secondary efficacy variables, namely SHAPS and SSI scores (p \leq 0.001 for both scales).

In general, adverse effects were mild, and vortioxetine augmentation was well tolerated. The most commonly reported adverse effects were nausea in seven subjects (24%, even if the drug was administered after a meal, usually breakfast), headache in three (12%), and dry mouth in two (5.6%).

Discussion

To date, the 36 subjects evaluated in our study were the largest sample of stage I TRD treated with vortioxetine augmentation for 8 weeks.

The results of our retrospective evaluation support the hypothesis that vortioxetine augmentation may be useful in relieving symptoms of stage I TRD. A statistically significant clinical improvement was reported after 4 weeks of treatment and continued until the end of the study.

The rates of response and remission during the study period were relatively high, corroborating the clinical relevance of the observed changes in HAM-D scores. Among patients who completed the study, the response rate was as high as 41.7%. Remission, in which depressed patients are indistinguishable from healthy subjects, was achieved by 33.3% of completers. Moreover, in our study, we found a remarkable effect of the vortioxetine-SSRI combination on anhedonia, which is consistent with a previous study.²⁰ Interestingly, in our sample, no patient had worsening of symptoms or increase in suicidal ideation.²¹ Instead, we found that the vortioxetine-SSRI combination was highly beneficial in reducing suicidal ideation, which may be a particularly important effect when treating MDD subjects with antidepressants, as also demonstrated in previous studies.²²

The vortioxetine-SSRI combination was also remarkably well tolerated. This may be partly explained by vortioxetine pharmacokinetics.²³ Vortioxetine is primarily metabolized by the CYP2D6 enzyme, and less so by CYP2C19, but, given that the ratios of maximum plasma concentration for the inhibitor (vortioxetine or its metabolites) and the dissociation constant of the inhibitor (Ki) were far below 0.1, the inhibition is considered clinically irrelevant.²³⁻²⁵ Nonetheless, it cannot be ruled out that concomitant use of vortioxetine and paroxetine may have resulted in increased plasma concentrations of the former as a result of significant CYP2D6 inhibition by the latter.

All considered, vortioxetine augmentation may be an option for the treatment of patients with stage I TRD, taking into account the favorable side-effect profile of this combination. Theoretically, the concomitant use of vortioxetine and an SSRI may boost serotonergic activity without further postsynaptic 5-HT_{2A} blockade (thus limiting the SSRI dose-related side effects).^{16,26} Moreover, the partial agonist effect of vortioxetine on the postsynaptic 5HT_{1B} heteroreceptors located in GABAergic interneurons may increase the release of glutamate in the hippocampus and prefrontal cortex, which may further contribute to an antidepressant effect.²⁷ This mechanism of action may also increase clinical efficacy in treating cognitive symptoms, which are frequently present in patients with suboptimal or inadequate response to antidepressants, and thus contribute to the achievement of complete remission in everyday clinical practice.^{12,28} Vortioxetine augmentation may also increase the release of dopamine, noradrenaline, and acetylcholine through the blockade of postsynaptic 5-HT_{1B} heteroreceptors, further explaining the observed efficacy on HAM-D scores.²⁹

The present exploratory study has several limitations, which include the small sample, the retrospective chart-review design, the absence of placebo or active control groups, and the short treatment period. Furthermore, data were only available after 1, 4, and 8 weeks, without intermediate comparisons, and the calculated p-values

must be considered in light of the small sample size. Therefore, further work with vortioxetine augmentation in placebo-controlled, randomized, double-blind clinical trials on larger samples are warranted.

In conclusion, add-on vortioxetine may be useful and relatively well tolerated in patients with stage I TRD. Future randomized controlled trials are needed.

Disclosure

The authors report no conflicts of interest.

References

- Tomasetti C, Montemitto C, Fiengo AL, Santone C, Orsolini L, Valchera A, et al. Novel pathways in the treatment of major depression: focus on the glutamatergic system. *Curr Pharm Des*. 2019;25:381-7.
- Muneer A. Mood disorders: practical issues in diagnosis and management. 1 online resource. Abingdon: Routledge; 2018.
- Han KM, De Berardis D, Fornaro M, Kim YK. Differentiating between bipolar and unipolar depression in functional and structural MRI studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;91:20-7.
- Kasper S, Frazer A. Editorial for treatment-resistant depression (TRD). *Int J Neuropsychopharmacol*. 2019;22:83-4.
- Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. *Can J Psychiatry*. 2010;55:126-35.
- Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, et al. Treatment resistant depression: a multi-scale, systems biology approach. *Neurosci Biobehav Rev*. 2018;84:272-88.
- Thase ME, Schwartz TL. Using mechanism of action to choose medications for treatment-resistant depression. *J Clin Psychiatry*. 2015;76:e1147.
- Stuhec M, Oravec R. Moclobemide as add-on therapy to agomelatine in a patient with treatment-resistant major depressive disorder: a psychopharmacological case. *Wien Klin Wochenschr*. 2016;128:295-8.
- Strawbridge R, Carter B, Marwood L, Bandelow B, Tsapekos D, Nikolova VL, et al. Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis. *Br J Psychiatry*. 2019;214:42-51.
- Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, et al. Defining treatment-resistant depression. *Depress Anxiety*. 2020;37:134-45.
- De Berardis D, Fornaro M, Valchera A, Cavuto M, Perna G, Di Nicola M, et al. Eradicating suicide at its roots: preclinical bases and clinical evidence of the efficacy of ketamine in the treatment of suicidal behaviors. *Int J Mol Sci*. 2018 Sep 23;19(10). pii: E2888. doi: 10.3390/ijms19102888.
- Orsolini L, Tomasetti C, Valchera A, Iasevoli F, Buonaguro EF, Fornaro M, et al. Current and future perspectives on the major depressive disorder: focus on the new multimodal antidepressant vortioxetine. *CNS Neurol Disord Drug Targets*. 2017;16:65-92.
- Orsolini L, Tomasetti C, Valchera A, Iasevoli F, Buonaguro EF, Velante F, et al. New advances in the treatment of generalized anxiety disorder: the multimodal antidepressant vortioxetine. *Expert Rev Neurother*. 2016;16:483-95.
- Kennedy SH, Grouin JM, Cadour S, Robert V, Picarel-Blanchot F. Relative short-term efficacy and acceptability of agomelatine versus vortioxetine in adult patients suffering from major depressive disorder. *Hum Psychopharmacol*. 2018 Jan;33(1). doi: 10.1002/hup.2646. Epub 2018 Jan 12.
- Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. 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. *Lancet*. 2018;391:1357-66.
- Citrome L. Vortioxetine for major depressive disorder: an indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord*. 2016;196:225-33.

- 17 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
- 18 Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry*. 1995;167:99-103.
- 19 Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979;47:343-52.
- 20 Cao B, Park C, Subramaniapillai M, Lee Y, Iacobucci M, Mansur RB, et al. The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. *Front Psychiatry*. 2019;10:17.
- 21 Larsson J. Antidepressants and suicide among young women in Sweden 1999-2013. *Int J Risk Saf Med*. 2017;29:101-6.
- 22 Courtet P, Lopez-Castroman J. Antidepressants and suicide risk in depression. *World Psychiatry*. 2017;16:317-8.
- 23 Chen G, Hojer AM, Areberg J, Nomikos G. Vortioxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet*. 2018; 57:673-86.
- 24 Matsuno K, Nakamura K, Aritomi Y, Nishimura A. Pharmacokinetics, safety, and tolerability of vortioxetine following single- and multiple-dose administration in healthy Japanese adults. *Clin Pharmacol Drug Dev*. 2018;7:319-31.
- 25 Chen G, Nomikos GG, Affinito J, Jacobson W, Zhao Z, Wang S, et al. Effects of intrinsic factors on the clinical pharmacokinetics of vortioxetine. *Clin Pharmacol Drug Dev*. 2018;7:880-8.
- 26 Sowa-Kucma M, Panczyszyn-Trzewik P, Misztak P, Jaeschke RR, Sendek K, Styczen K, et al. Vortioxetine: a review of the pharmacology and clinical profile of the novel antidepressant. *Pharmacol Rep*. 2017;69:595-601.
- 27 Salagre E, Grande I, Sole B, Sanchez-Moreno J, Vieta E. Vortioxetine: a new alternative for the treatment of major depressive disorder. *Rev Psiquiatr Salud Ment*. 2018;11:48-59.
- 28 De Berardis D, Olivieri L, Nappi F, Rapini G, Vellante F, Matarazzo I, et al. Vortioxetine and aripiprazole combination in treatment-resistant obsessive-compulsive disorder: a case report. *J Clin Psychopharmacol*. 2017;37:732-4.
- 29 Gonda X, Sharma SR, Tarazi FI. Vortioxetine: a novel antidepressant for the treatment of major depressive disorder. *Expert Opin Drug Discov*. 2019;14:81-9.