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Original Research

Vortioxetine as adjunctive therapy in the treatment of schizophrenia

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Abstract

Background: The evidence for safe and effective interventions to treat the negative and cognitive symptoms of schizophrenia is lacking.

Objectives: Vortioxetine is a novel antidepressant that has been used as adjunctive therapy for the treatment of psychosis; however, its effectiveness in clinical practice is relatively unknown. In this study, we aimed to determine the potential clinical effectiveness and safety and tolerability of vortioxetine in psychosis.

Design: This is a non-interventional, retrospective study on the add-on use of vortioxetine in a group of people with schizophrenia-spectrum disorders in a large UK NHS mental health trust.

Methods: Clinical effectiveness of vortioxetine was retrospectively assessed through the Clinical Global Impression – Severity (CGI-S) scale at 3 months. Safety and tolerability were evaluated through treatment discontinuation rates at 3, 6, and 12 months, and clinical reasons were evaluated at the primary endpoint of 3 months.

Results: Data were available for 40 subjects with a diagnosis of schizophrenia or schizoaffective disorder–prescribed vortioxetine treatment; 30 (75%) remained on treatment at 3 months. At CGI-S assessment, 15 of the 35 evaluated subjects reported at least a 1-point improvement, from 5 at baseline to 4 after 3 months of treatment. Twenty-six (65%) remained on treatment at 1-year follow-up. The main reasons for those discontinuing treatment were inadequate response (10%) and manic switch (7.5%), while one subject refused treatment. Tolerability to treatment was good, and 36 subjects (90%) reported no adverse events specific to vortioxetine treatment.

Conclusion: Schizophrenia is a complex illness, and there is insufficient treatment response in many individuals. A significant proportion of whom may require adjunctive treatments depending on the nature of the residual symptoms. Vortioxetine could be a potentially safe and effective option in such people, but further controlled studies are required.

Keywords: discontinuation, effectiveness, psychosis, schizophrenia, tolerability, vortioxetine

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Introduction

Antipsychotics have limited efficacy against negative and cognitive symptoms of schizophrenia.[1–4] Unfortunately, these are the symptoms that have been demonstrated to disproportionately impact functional recovery in people with schizophrenia.[5] The individuals with better cognitive functioning at stabilisation of their first episode of illness were more likely to achieve full recovery, adequate social and vocational functioning, and symptom remission.[6] More recent findings in people with treatment-resistant schizophrenia (TRS) demonstrated greater impairment in cognitive control compared to those who were treatment responsive, indicating both a possible non-dopaminergic mechanism in TRS and an avenue for therapeutic intervention.[7,8]

Antidepressants are commonly prescribed in the treatment of comorbid depression in people with schizophrenia. The prevalence of depression varies significantly between 7% and 75% in this

population.[9,10] Furthermore, antidepressants are often prescribed to overcome the burden of the negative symptoms, despite a paucity of robust findings supporting their benefit.[11] There are even less data on any effective pharmacological treatment of cognitive symptoms of schizophrenia.[12]

Vortioxetine is a novel multimodal antidepressant with a favourable adverse effect profile. Its mechanism of action is exerted through inhibition of the serotonin transporter (SERT), and modulation of specific serotonin (5-HT) receptors including 5-HT_{1A} (agonist), 5-HT_{1B} (partial agonist), and 5-HT_{1D}, 5-HT_3, 5-HT_7 (antagonist).[13] Through the modulation of serotonergic pathways, vortioxetine not only increases 5-HT release but also downstream noradrenergic, dopaminergic, cholinergic, histaminergic, and glutamatergic neurotransmission across the brain. It is unusual in the group of antidepressants in having demonstrated clinically meaningful cognitive improvement in different populations, an effect that was distinct from its antidepressant action.[14–16]

There is limited evidence on the use of vortioxetine in individuals with schizophrenia. A recent 8-week randomised controlled study in people with chronic schizophrenia demonstrated improvements in negative symptoms when vortioxetine was added to risperidone.[17] Work from our group in a small case series demonstrated the effectiveness of vortioxetine in those people with TRS when used as an adjunct to the antipsychotic lurasidone.[18] On this basis, there was an increase in the use of vortioxetine in schizophrenia within our trust, the South London and Maudsley NHS Foundation Trust (SLaM). We, therefore, conducted this exploratory study to establish the potential clinical effects and safety and tolerability of vortioxetine in people diagnosed with schizophrenia and schizoaffective disorder. In addition, we explore the reasons for vortioxetine prescription and report on the standard doses used in clinical care.

Methods

A non-interventional, observational, retrospective follow-up study design was employed to assess the clinical effectiveness of vortioxetine in subjects with schizophrenia or schizoaffective disorder. The primary objective was to evaluate the clinical impact of vortioxetine treatment initiation using the Clinical Global Impression – Severity (CGI-S) scale.[19] The secondary objective was to establish all-cause vortioxetine discontinuation rates.

Data source and ethical approval

The study used data from the SLaM Biomedical Research Centre (BRC) Case Register. SLaM is one of the United Kingdom's largest mental healthcare providers, delivering specialist inpatient and outpatient services to a local population of approximatively 1.3 million people.

Data were extracted using the Clinical Record Interactive Search (CRIS) system, an anonymised database containing electronic health records (EHRs) of service users referred to SLaM, fully described elsewhere.[20] Data were collected from anonymised medical notes from 2008 until 2019. Demographics and clinical data were extracted from both structured and unstructured fields within CRIS and from free text fields in medical records.

Study sample and data

The sample cohort was identified using the Generalised Architecture for Text Engineering (GATE) application. GATE is an open-source text analysis programme,[22] which drew together areas of free text from the SLaM Electronic Patient Journey System and the Maudsley Pharmacy database.

All subjects prescribed vortioxetine with a primary *International statistical classification of diseases and related health problems*: 10th revision (ICD-10)[23] diagnosis of schizophrenia (F20) or schizoaffective disorders (F25) at the time of vortioxetine initiation were identified. Both inpatients and outpatients were included with no specific age restriction. The date of vortioxetine initiation was defined as the date the subject was dispensed the first dose of vortioxetine.

Demographic and prescription data, including concomitant medication at vortioxetine initiation, were obtained from CRIS. Substance misuse was defined as reported illicit use of cocaine, cannabis, benzodiazepines, alcohol, and other substances including amphetamines and gamma-hydroxybutyrate (GHB). The CRIS notes were scrutinised for consideration of, or prior use of, clozapine treatment and was deemed to constitute evidence of treatment resistance. Reason for vortioxetine prescription, initiation date, dosage, and any recorded adverse reactions as well as a discontinuation date, where applicable, were recorded.

Outcomes

Clinical effectiveness. We used the CGI-S scale to retrospectively evaluate mental illness severity for individuals who had been initiated on vortioxetine as an adjunct to antipsychotic treatment for psychosis as the primary outcome. CGI-S scores were retrospectively assessed by two independent psychiatrists from anonymised medical notes, derived at two time points: at vortioxetine prescription and 3-month follow-up. Any discrepancies were resolved through consensus.

Treatment discontinuation. The secondary outcome measure of effectiveness was the proportion of people who remained on vortioxetine at 3-, 6-, and 12-month follow-ups after the first prescription, with the 3-month follow-up being the primary endpoint. Reasons for vortioxetine discontinuation were reported at 3-month as a proxy for tolerability, as current evidence suggests that most adverse events (and clinical improvements) occur within this period. Treatment discontinuation was defined as no vortioxetine prescription for at least 28 days.

Clinical reasons for prescription. The reasons for vortioxetine prescription were also explored to provide an indication of its potential clinical utilities. Specifically, we calculated the proportion of individuals who were initiated on vortioxetine to address affective, negative, cognitive, and refractory symptoms.

Vortioxetine dose and concurrent antipsychotics. Finally, we report the standard vortioxetine doses used in the clinical management of psychosis and the frequency of concomitant antipsychotic use.

Statistical analysis

Data were analysed using IBM SPSS Statistics (version 26). Descriptive statistics was used for the primary outcome of effectiveness and to analyse treatment continuation at 3-, 6-, and 12-month follow-ups, reasons for discontinuation, adverse effects, reasons for prescription, and antidepressant switch. Proportions and percentages for categorical data; means and standard deviations for continuous data; medians and interquartile ranges (IQRs) for skewed continuous data and ordinal data (e.g. CGI scores) were calculated. Kaplan–Meier survival curves were used to estimate and graph the time to vortioxetine discontinuation from prescription.

Results

Sample characteristics

Forty people with psychosis were identified for inclusion but follow-up data were unavailable for one person, leaving 39 SLaM patients who were prescribed vortioxetine between October 2015 and June 2019. As displayed in Table 1, mean (SD) age at vortioxetine prescription was 42.2 (13.35) years and 72.5% of the sample were male; 67.5% of the sample had a primary diagnosis of schizophrenia, and the mean (SD) duration of illness was 5.5 (5.83) years. In addition, 55% of the subjects had a diagnosis of TRS, and 82.5% were inpatients at the time of vortioxetine initiation. Subjects were categorised as TRS if they were previously or currently prescribed clozapine, or clozapine had been considered as a treatment option but was not initiated.

Clinical effectiveness

Full clinical data were available for 37 subjects for CGI-S assessments at baseline and at 3-month follow-up. The median CGI-S score for those people prescribed vortioxetine treatment was 5 (IQR = 5–6) at vortioxetine prescription compared with 4 (IQR = 4–5) at 3-month follow-up. CGI-S improved in 15 subjects but was unchanged in 20 individuals. Of note, 4 of the 15 subjects who improved on vortioxetine saw a 2-point improvement in CGI (Figure 1). In two people, CGI was assessed only at baseline and could not be evaluated at 3-month (Figure 1).

Treatment discontinuation

At 3-month follow-up, 30 (75%) subjects continued vortioxetine treatment, while 9 (22.5%) discontinued. Of these, 4 (10%) discontinued vortioxetine due to inadequate response, 3 (7.5%) due to manic switch, 1 (2.5%) due to worsening of his clinical presentation, and 1 (2.5%) refused the medication. Interestingly, 36 (90%) subjects did not report any specific adverse side effect.

At the long-term follow-ups, 29 (72.5%) people continued vortioxetine treatment at 6-month, and 26 (65%) at 1 year. These data are represented as a Kaplan–Meier survival plot in Figure 2.

Clinical reasons for prescription

Vortioxetine was initiated in majority of individuals to improve negative and affective symptoms

Table 1. Baseline clinical and demographic data.

		Mean (SD)	Frequency	Percent (%)
Age (years)	–	42.2 (13.35)	–	–
Duration of illness (years)	–	5.5 (5.83)	–	–
Gender	Male	–	29	72.5
	Female	–	11	27.5
Ethnicity	White	–	23	57.5
	Black/African/Caribbean	–	10	25.0
	Asian	–	4	10.0
	Mixed	–	2	5.0
Diagnosis	Schizophrenia	–	27	67.5
	Schizoaffective disorder	–	13	32.5
TRS	Treatment resistant	–	22	55.0
	Non-treatment resistant	–	18	45.0
Care setting	Inpatient	–	33	82.5
	Outpatient	–	7	17.5
Psychiatric comorbidity	No comorbidity	–	21	52.5
	Comorbidity	–	19	47.5
ECT	Concurrent ECT treatment	–	3	7.5
Substance abuse	Concurrent substance abuse	–	5	12.5
Alcohol dependence	Concurrent alcohol dependence	–	1	2.5

ECT, electroconvulsive therapy; SD, standard deviation; TRS, treatment-resistance schizophrenia.

($n = 30$, 75%). Vortioxetine was initiated specifically to improve cognition in seven individuals. In three people, it was initiated to improve resistant psychotic symptoms.

Twenty-one subjects (52.5%) started vortioxetine as first antidepressant, whereas 17 (42.5%) individuals were switched to vortioxetine from a previous antidepressant. In two cases (5.0%), vortioxetine was initiated as adjunct to a previous antidepressant.

Vortioxetine dose and concurrent antipsychotics

Vortioxetine is available for oral administration at doses between 5 and 20 mg/day. The initial and therapeutic vortioxetine dosage frequencies are displayed below in Table 2. Mean initial dose was 11.1 (SD = 4.310); mean final dose was 16.8 (SD = 4.606). The frequency of different concomitant antipsychotic treatment is described in Table 3. Vortioxetine was most frequently prescribed as an add-on to clozapine and lurasidone.

Discussion

Evidence for effectiveness of adjunctive antidepressant treatment of negative symptoms in schizophrenia is inconsistent. National Institute for Health and Care Excellence (NICE) guidelines stipulate that further studies are required

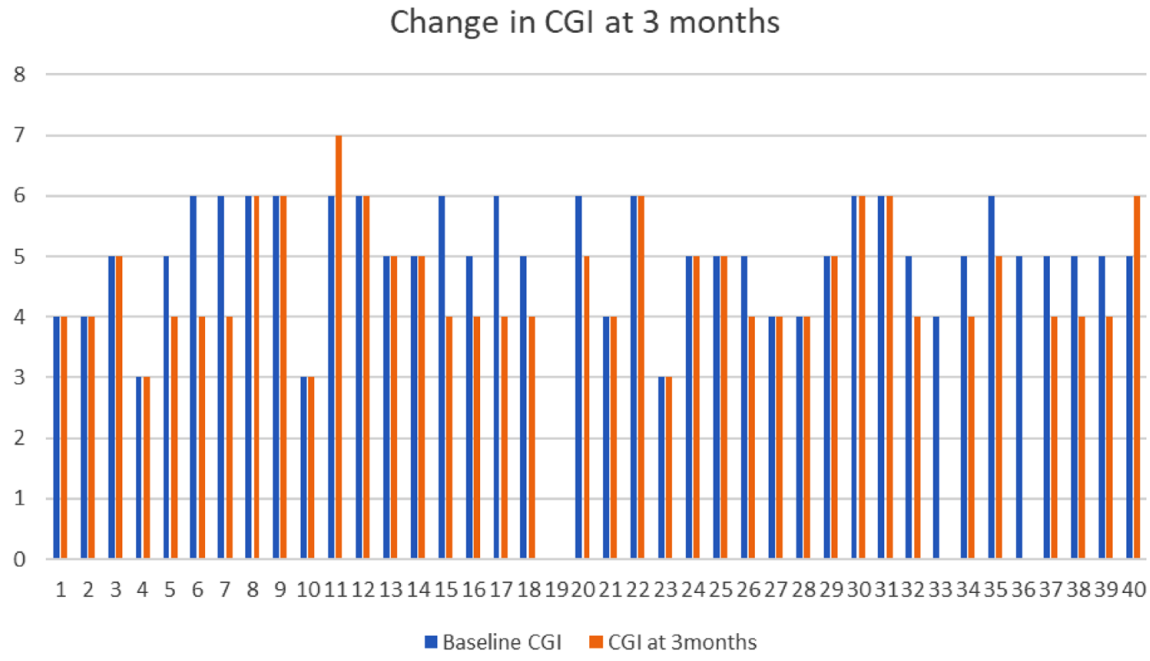

Figure 1. Change in CGI at 3-month follow-up.

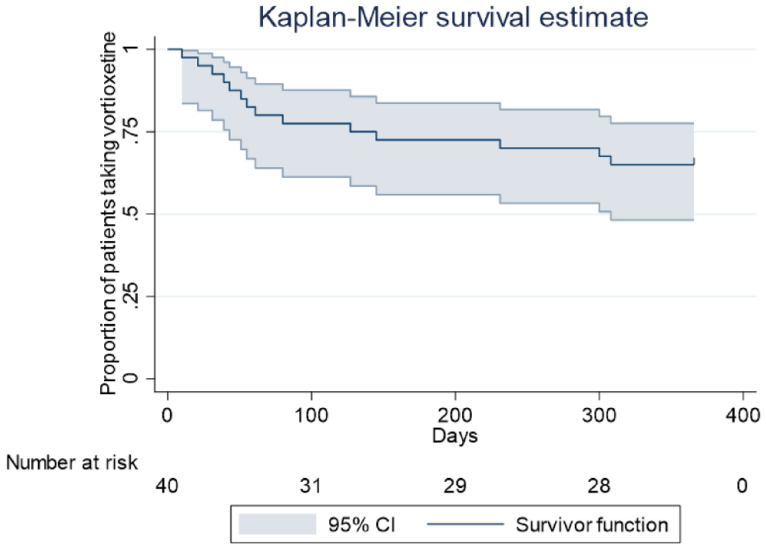

Figure 2. Kaplan–Meier plot showing the proportion of people (with 95% confidence interval) remaining on vortioxetine over a 1-year period.

to establish the clinical- and cost-effectiveness of antidepressants as adjuncts to treat persistent negative symptoms. In people with TRS, there is uncertainty regarding the evidence for the efficacy of clozapine in persistent negative symptoms and there are no such guidelines for the treatment of cognitive symptoms of schizophrenia.

Furthermore, people who have TRS may experience either ongoing positive symptoms of psychosis, ongoing negative symptoms, ongoing cognitive symptoms, or most frequently, a combination of ongoing symptoms in all three domains.[24] Unfortunately, treatment guidelines for TRS give no specific recommendations for people who fail to respond to clozapine, or

Table 2. Frequencies and proportions for vortioxetine initial and final dose.

	Frequency	Percent (%)
Vortioxetine initial dose		
Vortioxetine 5 mg	5	12.5
Vortioxetine 10 mg	27	67.5
Vortioxetine 15 mg	2	5.0
Vortioxetine 20 mg	6	15
Vortioxetine final therapeutic dose		
Vortioxetine 10 mg	12	30.0
Vortioxetine 15 mg	2	5.0
Vortioxetine 20 mg	26	65.0

Table 3. Antipsychotic therapies concurrent to vortioxetine treatment.

	Frequency	Percent (%)
Clozapine	8	20.0
Clozapine and other antipsychotics	13	32.5
Clozapine and amisulpride	2	5.0
Clozapine and aripiprazole	4	10.0
Clozapine and lurasidone	6	15.0
Clozapine, lurasidone, and amisulpride	1	2.5
Flupentixol	1	2.5
Lurasidone	6	15.0
Lurasidone and olanzapine	2	5.0
Olanzapine	3	7.5
Olanzapine, amisulpride, and haloperidol	1	2.5
Quetiapine	3	7.5
Risperidone	1	2.5
Zuclopenthixol	2	5.0

alternatives when clozapine is not tolerated. This is, perhaps, the greatest unmet need in the treatment of schizophrenia.

Although lacking precision, the primary indication for the initiation of vortioxetine in this study appears to be as adjunct to antipsychotics, especially clozapine (52.5%), in people with TRS. Vortioxetine was initiated primarily to address negative, affective, and cognitive symptoms, although in a substantial minority, it was initiated primarily to address, resistant psychotic symptoms.

At 3 months, median CGI-S improved from 5 (marked ill) to 4 (moderately ill), corresponding to an estimated improvement of 17 points on the Positive and Negative Symptoms Scale (PANSS).[25] Due to the sample size, we could not evaluate the impact of vortioxetine dose or the effect of specific antipsychotics on the effectiveness of the combination.

A recent study investigating vortioxetine as adjunct to risperidone found significant improvements in negative symptoms but not in positive symptoms.[17] On the contrary, a pilot study of vortioxetine on cognition in stable individuals with TRS stabilised on clozapine, demonstrated not only improvements in cognition, but significant reductions in positive symptoms.[26] Of course, there are notable differences between these studies. The vortioxetine–risperidone group was not treatment resistant and lasted only 8 weeks, whereas the clozapine group was treatment resistant and lasted for 24 weeks. It is thus feasible that there are significant time effects.

One of the main findings of our study is the good tolerability of vortioxetine in our cohort. Tolerability of antidepressants affects adherence to treatment. In our sample, continuation rate at 3-, 6-, and 12-month (77.5%, 72.5%, and 65%, respectively) are in line with other studies of vortioxetine in depressed individuals with completion rates of 50–73% at 12 months.[27] Early antidepressant discontinuation is a relatively common phenomenon, with one large study showing only 27.6% of people continued antidepressant therapy for more than 90 days,[28] and another showing only one out of five people complied with treatment for over 4 months.[29] It must be noted, however, that the majority of our subjects were initiated on vortioxetine as inpatients, which may partly explain the high adherence rates. Notwithstanding, 90% of the subjects reported no specific side effects.

All antidepressants are associated with the risk of manic exacerbation, with risk higher in people with bipolar disorder compared with major depressive disorder.[30] In our cohort, three subjects discontinued vortioxetine following development of a manic episode. As with other antidepressants, vortioxetine should be used with

caution in those with a history of mania and hypomania and should be discontinued in any individual entering a manic phase.

Limitations

There are some notable limitations to our study. First, we employed a naturalistic study design, and the assessment of clinical presentation was carried out retrospectively. In addition, the evaluation of changes in symptom severity was based on case note reviews, and it is naturally difficult to tease out the precise contribution of vortioxetine to overall symptom change. Other limitations include a lack of control group and small sample size; however, this is comparable to existent naturalistic studies. Furthermore, we did not review the reasons for discontinuation at 6 and 12 months, given that 3-month follow-up was chosen as the primary endpoint. This limits the generalisability of our findings regarding the long-term tolerability of vortioxetine in people with psychosis. Finally, the sample may not have been fully representative of the target population, given that peoples in this study were predominantly white, treatment-resistant inpatients with low rates of substance abuse.

Conclusion

In summary, we present preliminary data to suggest a trial of vortioxetine for resistant symptoms of schizophrenia, in individuals treated with antipsychotic medication including clozapine, with significant affective, cognitive, and positive symptoms; with a relatively benign side effect profile except for necessary monitoring for elevated mood in a small minority of subjects. Given the paucity of treatment options for treatment-resistant individuals after clozapine, vortioxetine offers one potentially useful option. This retrospective naturalistic study suggests that vortioxetine appears to be a safe and effective antidepressant as adjunct to antipsychotic treatment for residual negative and affective symptoms and holds some promise in positive and cognitive symptoms. More research is needed to elucidate the precise role and place in the treatment of schizophrenia.

Ethical approval and consent to participate

Oxfordshire Research Ethics Committee (08/H0606/71 + 5)[21] gave ethical approval for the use of CRIS as a research data set, and the CRIS oversight committee granted permission for this study. All methods were performed in accordance with relevant guidelines and regulations. The need for informed consent for this study was waived by SLaM Drug and Therapeutics Committee.

Consent for publication

Not applicable.

Author contributions

Sofia Redaelli: Data curation; Formal analysis; Writing – original draft.

Lilla Porffy: Data curation; Formal analysis; Supervision; Writing – review & editing.

Ebenezer Oloyede: Formal analysis; Methodology; Writing – review & editing.

Olubanke Dzahini: Formal analysis; Methodology; Writing – review & editing.

Gabriella Lewis: Formal analysis; Methodology; Writing – review & editing.

Maria Lobo: Formal analysis; Methodology; Writing – review & editing.

Eromona Whiskey: Conceptualisation; Supervision; Writing – review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

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