Original Paper

Vortioxetine as adjunctive therapy to risperidone for treatment of patients with chronic schizophrenia: A randomised, double-blind, placebo-controlled clinical trial

Journal of Psychopharmacology
1–8

DOI: 10.1177/0269881120909416
journals.sagepub.com/home/jop

Ehsan Mozen-Zadeh[1,2*], Samaneh Bayanati[1*], Kimia Ziafat[1,2], Farzin Rezaei[3], Bita Mesgarpour[4] and Shahin Akhondzadeh[1]

Abstract

Introduction and objectives: Vortioxetine, a novel antidepressant, may be an interesting candidate for adjunctive therapy of schizophrenia. Our primary objective was to investigate the effect of vortioxetine on negative symptoms, with the assessment of positive, general psychopathology and total symptoms as our secondary goal.

Methods: This was an eight-week randomised, double-blind, placebo-controlled, parallel-group clinical trial, in which 78 inpatients with chronic schizophrenia were stabilised with risperidone (4–6 mg/day) for two months before being assigned to adjunctive vortioxetine (10 mg b.i.d.) or placebo. The patients were assessed using the Positive and Negative Syndrome Scale (PANSS), Extrapyramidal Symptom Rating Scale and Hamilton Depression Rating Scale during the study course. All participants had a PANSS negative symptoms subscale score of ⩾16 at baseline. Sixty-eight patients completed the trial.

Results: Vortioxetine improved the negative symptoms score as the primary outcome and total PANSS score as a secondary outcome significantly better than placebo from baseline to end point at week 8, accompanied by significant time × treatment interactions and effect sizes (negative symptoms: mean difference (95% confidence interval (CI))=−1.82 (−2.73 to −0.92); total scores: mean difference (95% CI)=−2.09 (−3.16 to −1.01). No significant difference was detected for changes in positive symptoms score or PANSS general psychopathology score as the other secondary outcomes from baseline to end point between the two treatment arms. The incidence of adverse events was comparable between groups.

Conclusions: This is the first study to provide evidence for the therapeutic effect of vortioxetine on negative symptoms as an adjunctive to treatment with antipsychotics in patients with schizophrenia.

Keywords

Antidepressant, clinical trial, psychosis, schizophrenia, vortioxetine

Introduction

Schizophrenia is a chronic psychiatric disorder accompanied by high rates of morbidity and mortality and a high burden of disease (Akhondzadeh, 2001; Rössler et al., 2005; Saha et al., 2007; Świtaj et al., 2012). Routine antipsychotic regimens cause considerable adverse effects in patients with schizophrenia, and even in those who are compliant with their treatments, schizophrenia is associated with high levels of residual disease. Negative symptoms, in particular, are largely resistant to available treatments and a major disabling factor in this population (Bobes et al., 2010; Buckley and Stahl, 2007; Schooler et al., 2015).

In order to increase the response to antipsychotic treatments and improve negative symptoms in patients with schizophrenia, several different strategies have been studied (Chue and Lalonde, 2014) among which add-on antidepressant therapy is both an active line of research and a clinical practice in many parts of the world (Chue and Lalonde, 2014; Möller and Czobor, 2015). In fact, adjunctive antidepressant therapy has been a choice not only for the majority of patients with schizophrenia (Möller and Czobor, 2015; Remington et al., 2017) but also for refractory cases (Siskind et al., 2018). Meanwhile, the efficacy of adjunctive antidepressant therapy for schizophrenia has remained a matter of debate (Mao and Zhang, 2015), as previous systematic reviews and meta-analyses have rarely provided support for this strategy, while emphasising limitations of randomised clinical trials and the modest effect sizes for many of the studied antidepressants (Helfer et al., 2016; Terevnikov et al., 2015). Nevertheless, further research in this field is needed to assess previously studied medications better and potentially introduce new therapies (Akhondzadeh and Moazen-Zadeh, 2017; Helfer at al., 2016).

[1]Psychiatric Research Centre, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Psychiatry, Institute of Mental Health, University of British Columbia, Vancouver, Canada
[3]Qods Hospital, Kurdistan University of Medical Sciences, Sanandaj, Iran
[4]National Institute for Medical Research Development (NIMAD), Tehran, Iran

*These authors contributed equally to this work.

Corresponding author:
Shahin Akhondzadeh, Psychiatric Research Centre, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran, 13337, Iran.
Email: s.akhond@neda.net

Approved in 2013 by the Food and Drug Administration for the treatment of major depression, vortioxetine is an atypical antidepressant with a complex mechanism of action and prominent clinical effects, which has gained a lot of attention in research on depressive/anxiety disorders, while appearing to be an interesting candidate for adjunctive therapy in schizophrenia. The mechanism of action for vortioxetine has not been completely delineated, but available lines of evidence indicate it to have an inhibitory effect on serotonin transporter and a modulatory effect on several 5-HT receptors (Sowa-Kućma et al., 2017), with consequent enhanced release of other neurotransmitters, including acetylcholine, norepinephrine, histamine and dopamine (Stahl, 2015a, 2015b).

At the clinical level, vortioxetine is not only an effective and tolerable antidepressant for the treatment of acute major depressive disorder, according to a recently published comprehensive network meta-analysis comparing 21 antidepressants (Cipriani et al., 2018), but also an effective and tolerable option for switching therapy in those patients who are unable to tolerate or do not respond appropriately to their current treatment regimen (Brignone et al., 2016). Beyond its effects on depressive symptoms, vortioxetine has interestingly demonstrated beneficial effects on cognitive function, independent of improving depressive symptoms (Frampton, 2016), and has also been used successfully for the treatment of anxiety and panic disorders (Shah and Northcutt, 2018; Yee et al., 2018).

Based on the above-mentioned evidence, we aimed to assess the efficacy and adverse events of vortioxetine as an adjunctive therapy to antipsychotics in the treatment of patients with stable schizophrenia characterised by significant negative symptoms using a randomised clinical trial design. Our primary interest was the effect of vortioxetine on negative symptoms, with the assessment of positive, general psychopathology and total symptoms as our secondary goal.

Methods

Trial design and settings

This was an eight-week, randomised, double-blind, placebo-controlled, parallel-group clinical trial of vortioxetine in patients with schizophrenia who were referred to a large-scale academic psychiatry hospital (Roozbeh Hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran) from November 2017 to April 2019. The study was registered at the Iranian Registry of Clinical Trials (IRCT201710241556N100; http://www.irct.ir) after approval by the Institutional Review Board of TUMS in accordance with the World Medical Association code of ethics (IR.TUMS.VCR.REC.1396.3556; Declaration of Helsinki, as revised in Brazil 2013). All patients and their legally authorised representatives provided written informed consent, with full awareness of their ability to withdraw from the study at any time and without affecting their relationship with the health-care team.

Participants

To be eligible, treatment with a stable dose of risperidone for a minimum of eight weeks was required prior to entry. Patients were also required to be clinically stable for a minimum of four weeks prior to the study. The clinical stability was defined as no more than 20% change in consecutive ratings (one week apart) on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

Eligible candidates were male and female inpatients, aged 18–50 years, with chronic schizophrenia (⩾2 years) based on the Structured Clinical Interview for Diagnostic and Statistical Manual-5 Clinical Version (First et al., 2015), which was confirmed through an interview by a senior psychiatrist, as well as chart reviews. All participants had a PANSS negative symptoms subscale score of ⩾16 before the start of treatment with vortioxetine. Patients were excluded from study participation if any of the following criteria were met: alcohol/substance (except nicotine) use disorder based on DSM-5 or other co-morbid DSM-5 disorders, suicidal ideation, a score of ⩾4 on the depression item of PANSS, a score of ⩾14 on the 17-item Hamilton Depression Rating Scale (HDRS), a score of ⩾2 on the suicide item of HDRS, severe extrapyramidal symptoms, mental retardation determined by clinical judgement, inability to communicate, serious neurological or medical conditions, history of recent head traumas or previous neurological surgeries, pregnancy, lactation, women of child-bearing age not using reliable contraception, history of hypersensitivity to risperidone or vortioxetine, electroconvulsive therapy in the last two weeks prior to the study, history of liver disease or current use of medications with CYP450 inhibitory effects.

Interventions

Patients were assigned to risperidone (Risperdal; Janssen Pharmaceuticals, Beerse, Belgium) up to 6 mg/day during the course of the trial. Vortioxetine 10 mg twice daily or placebo (ACER, Tehran, Iran) were started after patients received risperidone for eight weeks and stabilised. During the trial, participants were required not to use a second antipsychotic, antidepressants, mood stabilisers or antihistamines, nor to receive behaviour intervention therapy. Reports by health-care personnel and family members were used to check for adherence.

Outcomes

The primary outcome was the difference in mean change for PANSS negative symptoms subscale score from baseline to the end point between the vortioxetine and placebo treatment arms. Secondary outcomes were defined as the difference in mean change for PANSS positive symptoms and general psychopathology subscale scores as well as PANSS total score from baseline to the end point between the two treatment arms.

The PANSS was the choice measure of treatment efficacy at each time point during the trial (i.e. weeks 0, 2, 4, 6 and 8). As a valid and reliable rating scale, the PANSS consists of 30 items concerning negative symptoms (7 items), positive symptoms (7 items) and general psychopathological symptoms (16 items) in schizophrenic patients (Kay et al., 1987). Each item is scored on a Likert scale from 1 to 7. We used the 17-item HDRS (Hamilton, 1960) to measure depressive symptoms. Both scales have been widely used in clinical trials of schizophrenia and previously applied in the Iranian population (Kashani et al., 2017; Tajik-Esmaeeli et al., 2017). Patients were rated by one of the

investigators, as well as a well-trained and experienced third-year resident of psychiatry.

Safety

The safety and tolerability of the study medications were assessed at weeks 0, 1, 2, 4, 6 and 8 using a comprehensive checklist of adverse effects of vortioxetine and risperidone prepared based on previous trials and expert opinion, followed by open-ended questions, thorough physical examination and Extrapyramidal Symptom Rating Scale (ESRS; part 1: parkinsonism, dystonia, dyskinesia; sum of 11 items; Chouinard and Margolese, 2005). The ESRS has previously been applied in Iranian clinical trials (Kashani et al., 2017; Moazen-Zadeh., 2017; Tajik-Esmaeeli et al., 2017). Furthermore, the nurses involved, as well as the participants and their caregivers, were required to report any unexpected symptoms or signs. Assessment of treatment adverse events and behavioural appraisals were done by independent trained and experienced raters during the trial. Adverse events were systematically evaluated at each time point using a 25-item checklist (Khajavi et al., 2012). Furthermore, patients were also asked an open-ended question about any adverse event that was not mentioned on the checklist. If a side effect was detected, the treatment would be continued, decreased or discontinued according to the opinion of a responsible expert psychiatrist.

Sample size

Using data from similar trials conducted previously in patients with schizophrenia (Kashani et al., 2017), a difference in change of negative symptoms score of 2, with a standard deviation of 2.5, a two-sided type I error of 0.05 and a power of 80% were considered for calculation of the sample size. A final sample size of 78 was estimated after accounting for a potential 20% drop-out rate for a primary sample size of 65.

Randomisation, allocation concealment and blinding

Equal randomisation of patients to the vortioxetine and placebo arms was achieved by computerised random-number generation, with random permuted blocks of four or six. To conceal the treatment allocation from patients and physicians, sequentially numbered, opaque and sealed envelopes were used by independent personnel. Study medications were dispensed in identical containers by an independent investigational drug pharmacist. Placebo tablets were prepared in an identical shape, colour and taste to vortioxetine tablets. The health-care providers and patients were blinded to the treatment allocations.

Statistical methods

We used IBM SPSS Statistics v19.0.0 (IBM Corp., Armonk, NY) for analyses, and SigmaPlot v12.2.0 (SYSTAT Software, Inc., San Jose, CA) for generating the plots. The Shapiro–Wilk test of normality was applied. Mean (standard deviation (*SD*) or 95% confidence intervals (95% CI)) and count (%) were reported for continuous and categorical variables, respectively. The Freeman–Halton extension of Fisher's exact test and the independent samples *t*-test were used as appropriate. Assumption of equality of variances was checked by Levene's test to correct the degree of freedom and *p*-value in case of violation. Cohen's d (95% CI) was the choice method of reporting effect size. Two-way repeated-measures analysis of variance (ANOVA) was used to assess time × treatment interaction effects, with the measurement time points and the treatment groups as the between-subjects and within-subjects factors, respectively. Last observation carried forward was the method of choice for missing data imputation. Assumption of sphericity was checked by Mauchly's test in order to apply Greenhouse–Geisser's correction in case of violation. Multiple testing effect was not a concern for the difference in mean subscale score change from baseline to end point, and the relevant *p*-values for this difference were interpreted in conjunction with time × treatment interaction effects, which are robust against multiple testing. Two-tailed *p*-values of <0.05 were considered significant in all analyses.

Results

Participants

After screening 128 patients, 78 were randomised to the treatment arms, with 34 patients completing the study in each treatment arm, who were considered for final analysis (Figure 1). No significant difference was detected between the two treatment arms in terms of baseline characteristics, including sociodemographics, duration of illness, previous antipsychotic treatments, PANSS subscale scores, HDRS scores or ESRS scores (Table 1). The mean doses of risperidone administered during this trial were 4.10 mg/day (*SD*=0.45 mg/day) and 4.15 mg/day (*SD*=0.38 mg/day) in the vortioxetine and placebo arms ($p > 0.05$).

Outcome

PANSS negative symptoms score. Baseline PANSS negative symptoms scores were comparable in the two treatment arms ($p=0.715$; Table 1). There was a significantly more negative symptoms score reduction from baseline to end point in the vortioxetine arm accompanied by a large effect size (mean difference = −1.82 (95% CI −2.73 to −0.92); Cohen's d = 0.97 (95% CI 0.47−1.48); Table 2 and Figure 2). A significant time × treatment interaction effect was also observed between the two treatment arms (two-way ANOVA with Greenhouse–Geisser correction: $F=10.45$ (df = 1.97, mean square = 18.39), $p=0.000$).

PANSS total score. Baseline PANSS total scores were comparable in the two treatment arms ($p=0.942$; Table 1). There was a significant difference in total score reduction from baseline to end point, favouring the vortioxetine arm, accompanied by a large effect size (mean difference = −2.09 (95% CI −3.16 to −1.01); Cohen's d = 0.95 (95% CI 0.45−1.45); Table 2 and Figure 2). Moreover, a significant time × treatment interaction effect was observed between the two treatment arms (two-way ANOVA with Greenhouse–Geisser correction: $F=11.72$ (df = 1.91, mean square = 27.37), $p=0.000$).

PANSS positive symptoms score. Baseline PANSS positive symptoms scores were comparable in the two treatment arms

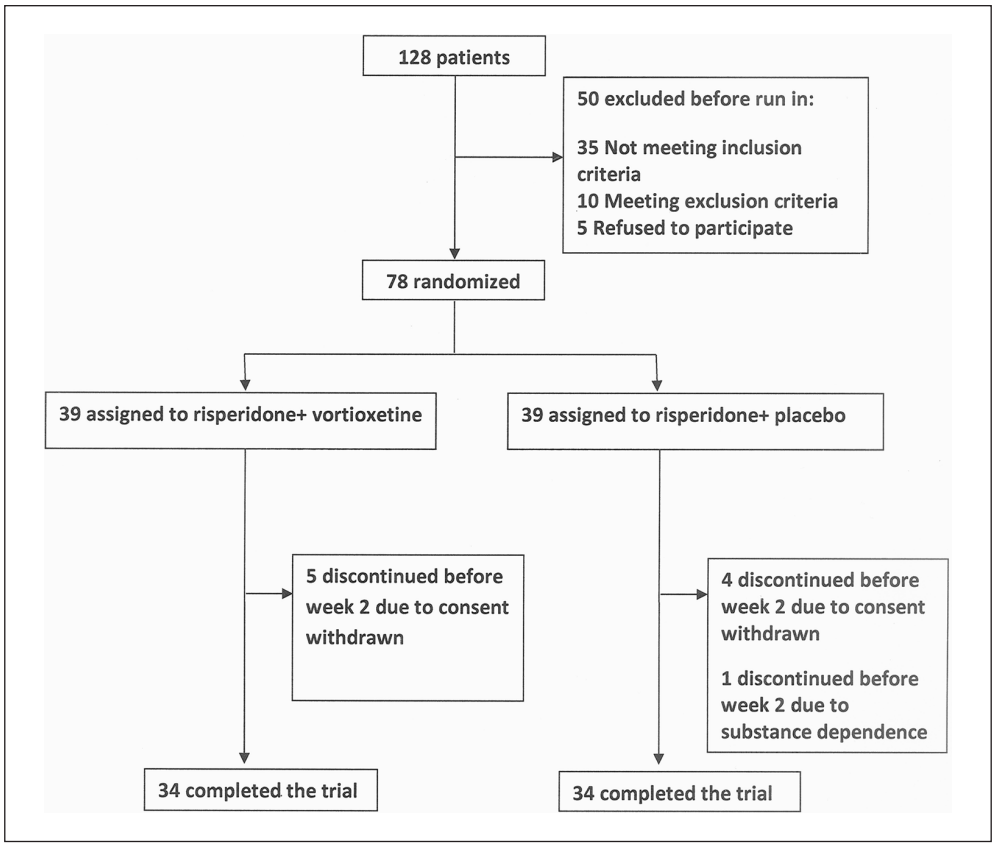

Figure 1. Flow diagram of patients with schizophrenia.

Table 1. Baseline characteristics of the patients with schizophrenia.

	Risperidone + vortioxetine (*N*=34)	Risperidone + placebo (*N*=34)	*p*-Value[a]
Age (years), *M* (*SD*)	34.44 (5.79)	32.88 (4.74)	0.229
Male:female, *n* (%)	24 (70.6%):10 (29.4%)	23 (67.6%):11 (32.4%)	0.800
Level of education, *n* (%)			
Under diploma	20 (58.8%)	19 (55.9%)	0.864
Diploma	10 (29.4%)	9 (26.5%)	
University degree	4 (11.8%)	6 (17.6%)	
Smoking, *n* (%)	28 (82.3%)	30 (88.2%)	0.519
Duration of illness (years), *M* (*SD*)	9.35 (4.45)	8.71 (3.82)	0.522
Previous antipsychotic medications, *n* (%)			
Risperidone	20 (58.8%)	21 (61.7%)	0.810
Halopridol	8 (23.5%)	9 (26.4%)	0.789
Fluphenazine	6 (17.64%)	7 (20.5%)	0.769
Olanzapine	7 (20.5%)	9 (26.4%)	0.584
Clozapine	3 (8.8%)	1 (2.9%)	0.364
HDRS score, *M* (*SD*)	8.18 (1.68)	8.03 (1.42)	0.698
ESRS score, *M* (*SD*)	1.29 (2.38)	1.41 (2.02)	0.827
PANSS score, *M* (*SD*)			
Negative symptoms	19.38 (3.36)	19.19 (3.15)	0.715
Total	48.06 (6.89)	48.18 (6.50)	0.942
Positive symptoms	9.68 (2.25)	9.24 (2.02)	0.398
General psychopathology	19.15 (4.12)	19.76 (5.04)	0.582

[a]Independent-samples *t*-test or Freeman–Halton extension of Fisher's exact test applied where appropriate.
SD: standard deviation; ESRS: Extrapyramidal Symptoms Rating Scale; HDRS: Hamilton Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale.

Table 2. Score changes from baseline for PANSS in patients with schizophrenia.

	M (*SD*) change from baseline		*M* (95% CI) difference in change	*t*-Value (df[a])	*p*-Value[a]
	Risperidone + vortioxetine (*N*=34)	Risperidone + placebo (*N*=34)			
PANSS negative symptoms					
Week 2	−0.18 (0.72)	0.03 (0.39)	−0.21 (−0.48 to 0.07)	−1.47 (66)	0.145
Week 4	−0.71 (1.31)	−0.35 (0.95)	−0.35 (−0.91 to 0.20)	−1.27 (60.06)	0.209
Week 6	−1.29 (1.92)	−0.41 (1.05)	−0.88 (−1.63 to −0.13)	−2.36 (51.13)	0.022
Week 8	−2.41 (2.24)	−0.59 (1.40)	−1.82 (−2.73 to −0.92)	−4.02 (55.19)	<0.001
PANSS total score					
Week 2	−0.24 (0.92)	−0.06 (0.24)	−0.18 (−0.51 to 0.15)	−1.08 (37.40)	0.287
Week 4	−0.74 (1.38)	−0.44 (0.86)	−0.29 (−0.85 to 0.26)	−1.06 (55.32)	0.295
Week 6	−1.94 (1.98)	−0.76 (1.10)	−1.18 (−1.96 to −0.40)	−3.02 (51.61)	0.004
Week 8	−3.15 (2.74)	−1.06 (1.50)	−2.09 (−3.16 to −1.01)	−3.897 (51.04)	<0.001
PANSS positive symptoms					
Week 2	0.09 (0.51)	0.00 (0)	0.09 (−0.09 to 0.27)	1.00 (33.00)	0.325
Week 4	0.09 (0.51)	0.00 (0)	0.09 (−0.09 to 0.27)	1.00 (33.00)	0.325
Week 6	−0.21 (1.01)	−0.15 (0.50)	−0.06 (−0.44 to 0.33)	−0.31 (66)	0.762
Week 8	−0.26 (1.02)	−0.21 (0.59)	−0.06 (−0.46 to 0.35)	−0.29 (66)	0.773
PANSS general psychopathology					
Week 2	−0.12 (0.48)	0.00 (0)	−0.12 (−0.28 to 0.05)	−1.44 (33.00)	0.160
Week 4	−0.12 (0.48)	0.00 (0)	−0.12 (−0.28 to 0.05)	−1.44 (33.00)	0.160
Week 6	−0.50 (1.05)	−0.09 (0.29)	−0.41 (−0.79 to −0.03)	−2.20 (37.92)	0.034
Week 8	−0.56 (1.21)	−0.15 (0.50)	−0.41 (−0.86 to 0.04)	−1.83 (43.96)	0.074

[a]Levene's test for assessment of equality of variances was the basis for the calculation of degree of freedom and concordant *p*-value.
CI: confidence interval; df: degrees of freedom.

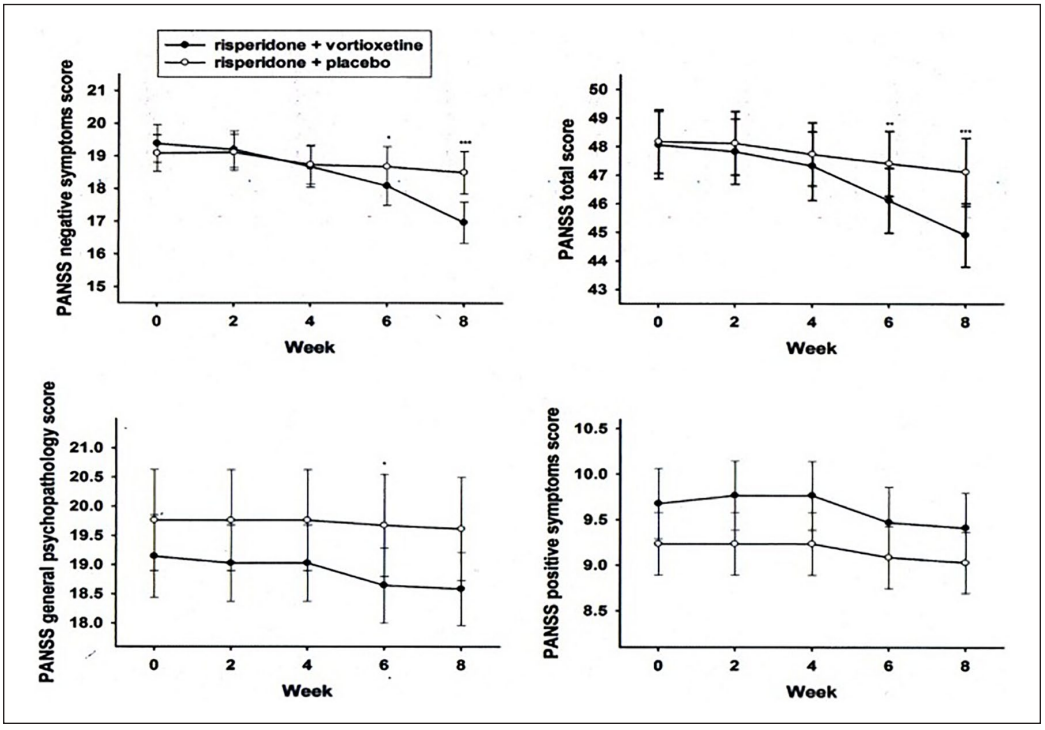

Figure 2. Trajectories of Positive and Negative Syndrome Scale (PANSS) scores in patients with schizophrenia according to the treatment arm. Plots represent mean score ± standard error of the mean at each time point.
*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ based on independent-samples *t*-test for comparison of the mean score change from baseline to each time point between the two treatment arms.

Table 3. Incidence of adverse events in patients with schizophrenia.

Side effect	Risperidone + vortioxetine (*N*=34)	Risperidone + placebo (*N*=34)
Drowsiness, *n* (%)	4 (11.8%)[a]	4 (11.8%)
Dizziness, *n* (%)	4 (11.8%)	2 (5.8%)
Constipation, *n* (%)	3 (8.8%)	4 (11.8%)
Diarrhoea, *n* (%)	3 (8.8%)	2 (5.9%)
Flatulence, *n* (%)	4 (11.8%)	3 (8.8%)
Nausea, *n* (%)	4 (11.8%)	2 (5.9%)
Vomiting, *n* (%)	5 (14.7%)	4 (11.8%)
Dry mouth, *n* (%)	4 (11.8%)	3 (8.8%)

[a]Fisher's exact test was used.

(p=0.398; Table 1). No significant difference was detected in positive symptoms score changes from baseline to end point between the two treatment arms (mean difference=−0.06 (95% CI −0.46 to 0.35); Cohen's d=0.06 (95% CI −0.42 to 0.54); Table 2 and Figure 2). Also, no significant time × treatment interaction effect was observed (two-way ANOVA with Greenhouse–Geisser correction: F=0.50 (df=1.42, mean square=0.26), p=0.545).

PANSS general psychopathology score. Baseline PANSS general psychopathology scores were comparable in the two treatment arms (p=0.582; Table 1). No significant difference was detected in general psychopathology score reduction from baseline to end point between the two treatment arms (mean difference=−0.41 (95% CI −0.86 to 0.04); Cohen's d=0.44 (95% CI −0.04 to 0.92); Table 2 and Figure 2). Also, no significant time × treatment interaction effect was observed (Two-way ANOVA with Greenhouse–Geisser correction: F=3.31 (df=1.25, mean square=1.95), p=0.063).

HRSD score. No significant difference was detected in HDRS score changes from baseline to end point between the two treatment arms (mean difference=−0.26 (95% CI −1.04 to 0.51), t (df)=0.68 (66), p=0.497).

ESRS score. No significant difference was detected in ESRS score changes from baseline to end point between the two treatment arms (mean difference=0.00 (95% CI 0)).

Adverse events. The distribution of incidence of adverse events was comparable in the two treatment arms, with no significant difference (Table 3).

Discussion

Negative symptoms of schizophrenia are usually resistant to the available antipsychotic treatments which is a major cause of disability in affected patients (Buckley and Stahl, 2007; Bobes et al., 2010; Schooler et al., 2015). Currently, the efficacy of add-on antidepressant therapy is actively investigated whilst already being implemented as common practice for these patients worldwide (Chue and Lalonde, 2014; Möller and Czobor, 2015). Vortioxetine is an atypical antidepressant which has gained much attention in research on depressive disorders and may be an interesting candidate as an add-on treatment strategy in schizophrenia. In this study, patients with schizophrenia who were randomised to receive vortioxetine experienced more improvement in terms of negative symptoms as well as overall symptoms from baseline to end point, which was confirmed by significant time × treatment interactions as well as a statistically significant but clinically minimal difference in score changes of approximately 2 points. However, there was no effect of either treatment on positive symptoms and general psychopathology.

To the best of our knowledge, this is the first report of treatment with vortioxetine in patients with schizophrenia. Considering that vortioxetine is an atypical antidepressant with a unique and complex mechanism of action but relatively similar clinical effects as other antidepressants, our findings are better compared to the totality of evidence on efficacy of antidepressants in treatment of patients with schizophrenia, rather than being compared to any specific medication or single clinical trial. In this regard, our findings are in line with the largest meta-analysis of antidepressant adjunctive therapy in patients with any of schizophrenia/schizophreniform/schizoaffective disorders by far, which included 82 RCTs and 3608 participants (Helfer et al., 2016). In their study, Helfer et al. (2016) reported that antidepressants were more effective than placebos in improving various symptoms, with the negative symptoms (standardised mean difference (SMD)=−0.30 (95% CI −0.44 to −0.16)) showing more prominent improvement than overall symptoms (SMD=−0.24 (95% CI −0.39 to −0.09)) or positive symptoms (SMD=−0.17 (95% CI −0.33 to −0.01)) where SMD in their meta-analysis was comparable to Cohen's d in our study. Another more recent meta-analysis of 42 clinical trials (Galling et al., 2018) only included double-blind antidepressant augmentation studies of continued antipsychotics in schizophrenia and thus was more similar to our study in terms of the included population as well as intervention compared to the study by Helfer et al. (2016). This recent meta-analysis also demonstrated improvement of negative symptoms (SMD=−0.28 (95% CI −0.47 to −0.09)) more than total symptoms (SMD=−0.37 (95% CI −0.57 to −0.17)), while no significant improvement in positive symptoms (SMD=−0.11 (95% CI −0.26 to 0.08)) was observed. Meanwhile, the two aforementioned meta-analyses, as well as a previous systematic review (Terevnikov et al., 2015), have emphasised their limitations, including but not limited to small sample sizes of the RCTs, heterogeneity of studied populations and different mechanisms of actions of the included antidepressants.

In this study, we did not investigate neurobiological effects of vortioxetine in schizophrenia, but some available lines of evidence may help to guide future research in this regard. The mechanism of action of vortioxetine is not completely understood. However, vortioxetine has been characterised as a serotonin reuptake inhibitor that, additionally, modulated the activity of several 5-HT receptors (Sowa-Kućma et al., 2017), with consequent enhanced release of other neurotransmitters, including acetylcholine, norepinephrine, histamine and dopamine (Stahl, 2015a, 2015b). Recent research conceptualised the multimodal action of vortioxetine as being region specific in the brain, especially for GABA and glutamate neurotransmitters (Pehrson et al., 2016). This region specificity together with vortioxetine effects on multiple neurotransmitters, including dopamine, has potential implications for application in schizophrenia, which is characterised by dopamine system activity alterations in different brain regions, causing different symptom categories (i.e. positive and negative symptoms; Akhondzadeh, 2001). Furthermore, vortioxetine has

demonstrated anti-inflammatory and immunomodulatory effects on human monocytes/macrophages (Talmon et al., 2018). An increased inflammatory response has been documented in patients with schizophrenia and especially in those with more antidepressant consumption (Fond et al., 2016), which has resulted in a category of novel therapeutics for schizophrenia targeting the immune system.

There are several limitations to our study. First, although powered enough to detect the between-groups differences, our sample size was relatively small to generalise the findings and provide firm clinical implications. Second, we had restrictive inclusion/exclusion criteria, and all patients were treated with the same antipsychotic (i.e. risperidone) which necessitates caution in terms of generalisability of our findings but simultaneously increases the reliability of our findings by controlling for confounders. Third, we did not use a measure of cognition to assess the cognitive therapeutic effects of vortioxetine, though previous trials on major depressive disorder have demonstrated unique effects of this drug in improving cognitive symptoms. Also, we did not consider measures of patients' subjective perspectives or functioning, or additional more comprehensive measures of negative symptoms such as the Scale for Assessment of Negative Symptoms. Fourth, the statistically significant effect sizes found in our study are relatively small in terms of clinical importance. Meanwhile, it is important to note that when it comes to persistent negative symptoms in patients who are already receiving antipsychotics, usually even minimal significant improvements are of interest in the initial short-term investigations. Furthermore, whether continuing vortioxetine beyond eight weeks could result in larger effect sizes remains a question to be answered in future studies, as the duration of this study was relatively short. Nevertheless, one of the strengths of our study was that patients were stabilised on risperidone before administration of vortioxetine was started, and they were also assessed for depressive symptoms at baseline and the end point, which showed no significant change. In this way, we were able to alleviate substantially the concern that the changes observed in negative symptoms score could also be attributed to the changes in depressive symptoms or positive symptoms in part, as these later symptoms may contribute to the severity of the primary negative symptoms in patients who are not stabilised on antipsychotic treatment and thus result in so-called secondary negative symptoms.

Conclusions

In conclusion, this study provides the first evidence on potential therapeutic effects of vortioxetine as an adjunctive antidepressant to antipsychotics in the treatment of patients with schizophrenia. Considering the limitations of this study and the available evidence on other antidepressants as adjunctive therapy in schizophrenia, future well-controlled studies are necessary to compare the efficacy of vortioxetine to other antidepressants. In particular, it would be interesting to demonstrate these therapeutic effects in a more general sample of patients.

Acknowledgements

This research was performed in support of the postgraduate thesis of Dr Samaneh Bayanati for the Iranian Board of Psychiatry under the supervision of Prof. Shahin Akhondzadeh.

Declaration of conflicting interests

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

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported by a grant to Prof. Shahin Akhondzadeh (grant number 35647) from Tehran University of Medical Sciences (TUMS). TUMS had no role in the design, conduct, data collection, analysis, data interpretation, manuscript preparation, review, final approval or the decision to submit the paper for publication.

ORCID iD

Shahin Akhondzadeh https://orcid.org/0000-0002-2277-5101

Supplemental material

Supplemental material for this article is available online.

References

Akhondzadeh S (2001) The 5-HT hypothesis of schizophrenia. *IDrugs* 4: 295–300.

Akhondzadeh S and Moazen-Zadeh E (2017) More ACTIONS needed to reach a consensus on adjunctive antidepressant therapy for negative symptoms of schizophrenia. *Evid Based Ment Health* 20: e3.

Bobes J, Arango C, Garcia-Garcia M, et al. (2010) Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. *J Clin Psychiatry* 71: 280–286.

Brignone M, Diamand F, Painchault C, et al. (2016) Efficacy and tolerability of switching therapy to vortioxetine versus other antidepressants in patients with major depressive disorder. *Curr Med Res Opin* 32: 351–366.

Buckley PF and Stahl SM (2007) Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? *Acta Psychiatr Scand* 115: 93–100.

Chouinard G and Margolese HC (2005) Manual for the extrapyramidal symptom rating scale (ESRS). *Schizophr Res* 76: 247–265.

Chue P and Lalonde JK (2014) Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. *Neuropsychiatr Dis Treat* 10: 777–789.

Cipriani A, Furukawa TA, Salanti G, et al. (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. *Lancet* 391: 1357–1366.

First MB, Williams JB, Karg RS, et al. (2015) *User's Guide to Structured Clinical Interview for DSM-5 Disorders (SCID-5-CV) Clinical Version*. Arlington, VA: American Psychiatric Publishing.

Fond G, Godin O, Brunel L, et al. (2016) Peripheral sub-inflammation is associated with antidepressant consumption in schizophrenia. results from the multi-center FACE-SZ data set. *J Affect Disord* 191: 209–215.

Frampton JE (2016) Vortioxetine: a review in cognitive dysfunction in depression. *Drugs* 76: 1675–1682.

Galling B, Vernon JA, Pagsberg AK, et al. (2018) Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia. *Acta Psychiatr Scand* 137: 187–205.

Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23: 56–62.

Helfer B, Samara MT, Huhn M, et al. (2016) Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. *Am J Psychiatry* 173: 876–886.

Kashani L, Shams N, Moazen-Zadeh E, et al. (2017) Pregnenolone as an adjunct to risperidone for treatment of women with schizophrenia: a randomized double-blind placebo-controlled clinical trial. *J Psychiatr Res* 94: 70–77.

Kay SR, Fiszbein A and Opler LA (1987) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 13: 261–276.

Khajavi D, Farokhnia M, Modabbernia A, et al. (2012) Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 73: 1428–1433.

Mao YM and Zhang MD (2015) Augmentation with antidepressants in schizophrenia treatment: benefit or risk. *Neuropsychiatr Dis Treat* 11: 701–713.

Moazen-Zadeh E, Shirzad F, Karkhaneh-Yousefi MA, et al. (2018) Simvastatin as an adjunctive therapy to risperidone in treatment of autism: a randomized, double-blind, placebo-controlled clinical trial. *J Child Adolesc Psychopharmacol* 28: 82–89.

Möller HJ and Czobor P (2015) Pharmacological treatment of negative symptoms in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 265: 567–578.

Pehrson AL, Jeyarajah T and Sanchez C (2016) Regional distribution of serotonergic receptors: a systems neuroscience perspective on the downstream effects of the multimodal-acting antidepressant vortioxetine on excitatory and inhibitory neurotransmission. *CNS Spectr* 21: 162–183.

Remington G, Addington D, Honer W, et al. (2017) Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry* 62: 604–616.

Rössler W, Salize HJ, Van Os J, et al. (2005) Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol* 15: 399–409.

Saha S, Chant D and Mcgrath J (2007) A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 64: 1123–1131.

Schooler NR, Buchanan RW, Laughren T, et al. (2015) Defining therapeutic benefit for people with schizophrenia: focus on negative symptoms. *Schizophr Res* 162: 169–174.

Shah A and Northcutt J (2018) An open-label, flexible dose adaptive study evaluating the efficacy of vortioxetine in subjects with panic disorder. *Ann Gen Psychiatry* 17: 19.

Siskind DJ, Lee M, Ravindran A, et al. (2018) Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. *Aust N Z J Psychiatry* 52: 751–767.

Sowa-Kućma M, Pańczyszyn-Trzewik P, Misztak P, et al. (2017) Vortioxetine: a review of the pharmacology and clinical profile of the novel antidepressant. *Pharmacol Rep* 69: 595–601.

Stahl SM (2015a) Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): blocking 5HT3 receptors enhances release of serotonin, norepinephrine, and acetylcholine. *CNS Spectr* 20: 455–459.

Stahl SM (2015b) Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): actions at serotonin receptors may enhance downstream release of four pro-cognitive neurotransmitters. *CNS Spectr* 20: 515–519.

Świtaj P, Anczewska M, Chrostek A, et al. (2012) Disability and schizophrenia: a systematic review of experienced psychosocial difficulties. *BMC Psychiatry* 12: 193.

Tajik-Esmaeeli S, Moazen-Zadeh E, Abbasi N, et al. (2017) Simvastatin adjunct therapy for negative symptoms of schizophrenia: a randomized double-blind placebo-controlled trial. *Int Clin Psychopharmacol* 32: 87–94.

Talmon M, Rossi S, Pastore A, et al. (2018) Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. *Br J Pharmacol* 175: 113–124.

Terevnikov V, Joffe G and Stenberg JH (2015) Randomized controlled trials of add-on antidepressants in schizophrenia. *Int J Neuropsychopharmacol* 18: pii: pyv049.

Yee A, Ng CG and Seng LH (2018) Vortioxetine treatment for anxiety disorder: a meta-analysis study. *Curr Drug Targets* 19: 1412–1423.