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A controlled study of the efficacy and safety of tandospirone citrate combined with escitalopram in the treatment of vascular depression: A pilot randomized controlled trial at a single-center in China

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ABSTRACT

Vascular depression can respond poorly to antidepressants. This study aimed to explore the efficacy and safety of tandospirone plus escitalopram for treating vascular depression with anxiety. This pilot randomized controlled trial included consecutive inpatients/outpatients with vascular depression/anxiety at the Department of Neurology, Fujian Medical University Union Hospital, China (January 2014 to December 2016). Among 157 patients screened, 100 were randomly divided into the tandospirone + escitalopram (combination therapy) and escitalopram (monotherapy) groups equally, and then followed for 8 weeks. Efficacy was evaluated using the Hamilton Depression (HAMD), Hamilton Anxiety (HAMA), Clinical Global Impression (CGI) and Mini-Mental State examination (MMSE) scales. Adverse events (AEs) were assessed with the Treatment Emergent Symptom Scale (TESS). HAMD and HAMA scores decreased progressively, showing reductions versus baseline at 1, 2, 4 and 8 weeks in both groups ($P < 0.001$). HAMD and HAMA scores were lower in the tandospirone + escitalopram group than those in the escitalopram group at 1 and 2 weeks ($P < 0.001$), but not at 4 and 8 weeks. Improvements in CGI scores (severity, improvement and efficacy indexes) were greater in the tandospirone + escitalopram group than that in the escitalopram group at 1 and 2 weeks ($P < 0.01$), but not at 4 and 8 weeks. The tandospirone + escitalopram group had higher MMSE scores than that in the escitalopram group at 4 and 8 weeks ($P < 0.01$). All AEs were mild, and the rates were comparable between groups. Augmentation of escitalopram with tandospirone accelerates the onset of anti-depressive and anxiolytic effects and improves cognitive function in patients with vascular depression and anxiety.

1. Introduction

Vascular depression is a subtype of depression that was first proposed in 1997 (Alexopoulos et al., 1997; Krishnan et al., 1997) and affects 3.4% of adults aged ≥50 years (Gonzalez et al., 2012). Cerebrovascular disease can cause vascular damage and abnormal neurotransmitter metabolism in the frontal-subcortical pathway, which is involved in emotional regulation and cognitive function, thereby causing depression (Alexopoulos et al., 1997; Krishnan et al., 1997). Vascular depression has clinical manifestations (such as psychomotor slowing, cognitive deficits, lack of insight and apathy) and features (i.e. a medical history of hypertension and no family history of depression) that are distinct from those of non-vascular depression in the elderly (Aizenstein et al., 2016; Taylor et al., 2013). Vascular depression is also associated with characteristic findings on magnetic resonance imaging (Aizenstein et al., 2016). Although the exact mechanisms underlying the pathogenesis of vascular depression remain unclear, it has been proposed that disruption of neural connectivity, inflammation, and hypoperfusion may all contribute to the process of vascular depression (Taylor et al., 2013).

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) that has been reported to show efficacy in depression (Cipriani et al., 2009a; Pastoor and Gobburu, 2014; Moller et al., 2010; Mohamed et al., 2006). Since the depressive symptoms are frequently combined with anxiety and cognitive impairments, patients with vascular depression often respond less well to standard antidepressant therapy (Naarding and

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Beekman, 2012). It is critical that novel treatment strategies are developed which are more effective and have a faster onset of action. Augmentation with nimodipine (a calcium channel blocker) results in a greater reduction of depressive symptoms and lower rates of recurrence in patients with vascular depression treated with standard antidepressants (Taragano et al., 2001). Additionally, accumulating evidence indicates that anxiolytic drugs may be a good choice for augmenting SSRI therapy (Kanba, 2004).

Tandospirone is a third generation anxiolytic that has been widely used in clinical practice for the treatment of various chronic anxiety disorders (Huang et al., 2017). Tandospirone has been shown to improve depressive symptoms in patients with dementia (Masuda et al., 2002). Furthermore, tandospirone exerts a synergistic effect with antidepressants in patients with major depressive disorder (MDD) (Lin et al., 2018). However, it remains unknown whether tandospirone can augment the effects of SSRI therapy in patients with vascular depression.

We hypothesized that tandospirone would augment the effects of escitalopram in patients with vascular depression and anxiety symptoms. Therefore, the aim of this pilot study was to compare clinical efficacy and safety between escitalopram monotherapy and escitalopram combined with tandospirone in patients with vascular depression and anxiety.

2. Materials and methods

2.1. Study design and patients

This pilot, single-blinded, randomized controlled trial included consecutive inpatients and outpatients with vascular depression combined with anxiety seen at the Department of Neurology, Fujian Medical University Union Hospital (Fuzhou, China) between January 2014 and December 2016. The inclusion criteria were: 1) met the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria (American Psychiatric Association, 2000) for a first-episode or relapse of MDD; 2) 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1980) score > 17; 3) Hamilton Anxiety Rating Scale (HAMA) score (Hamilton, 1959) ≥ 14; 4) met the diagnostic criteria for vascular depression proposed by Alexopoulos et al., (1997); 5) no impairment of consciousness; and 6) able to independently complete the various assessment scales. The exclusion criteria were: 1) a previous history of, or currently suffering with, other psychiatric diseases, except for depression or anxiety; 2) other severe or unstable systemic disorders such as heart, liver, kidney, endocrine, hematologic or respiratory disease; 3) allergy to tandospirone; 4) risk for suicide, which was evaluated using the Suicide Assessment Scale (Waern et al., 2010); 5) clinically significant abnormalities of the electrocardiogram or laboratory investigations; 6) alcohol or drug dependence during the past year was evaluated using the Michigan Alcoholism Screening Test (Powers and Spickard, 1984), which was also validated in geriatric outpatients (Hirata et al., 2001), and according to the ICD-10 (World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines.); 7) participated in other clinical studies during the previous 30 days; 8) hospitalization for a comorbid condition during the study (as comorbidities and their treatment can aggravate anxiety and depression); or 9) poor adherence to therapy, as assessed using the Morisky Medication Adherence Scale-8 (MMAS-8; maximum score: 8 points) (Morisky et al., 2008): a patient was excluded if they were consistently evaluated as showing poor adherence (score < 6 points) by two assessors.

The ethics committee of our hospital approved the present study (approval number: 2013038). All patients provided informed written consent for their inclusion in the study.

2.2. Calculation of sample size

As this was a pilot study, no formal calculation of sample size was performed. However, the study aimed to enroll a total of 100 patients.

2.3. Patient grouping

According to the above criteria, 100 patients were included. The patients were randomly divided into two groups, a tandospirone + escitalopram group (to receive combination therapy with tandospirone and escitalopram) and an escitalopram group (to receive escitalopram alone), using a computer-generated random number table (SPSS 13.0; SPSS Inc., Chicago, IL, USA). The patients and the investigators who allocated the patients to the groups were not blinded to the treatment used. However, the investigators performing all evaluations of efficacy and safety (a senior doctor and an associate chief physician) were blinded to the patient grouping.

2.4. Administration of drug therapy

Any drugs that the patient had been taking before inclusion in the study were stopped for 1-week (washout period) before the study drug (s) were initiated. Patients in the tandospirone + escitalopram group received escitalopram (10 mg, once daily; H. Lundbeck A/S, Copenhagen, Denmark); tandospirone (5 mg, 3 times daily; Sumitomo Dainippon Pharma Co. Ltd, Osaka, Japan) was added during the first week, and the dose was increased (to 10 mg, 3 times daily) in the second week. Patients in the escitalopram group received escitalopram alone (10 mg, once daily). The treatment course for both groups was 8 weeks. If a patient developed gastrointestinal adverse events (AEs) after taking escitalopram, the dose was initially reduced to 5 mg once daily for 3 days and then increased back to 10 mg once daily for maintenance therapy.

The following drugs were prohibited from being used during the study protocol: triptans, antipsychotics, monoamine oxidase inhibitors and beta-blockers. The following drugs were permitted: antiplatelet drugs, anticoagulant drugs, B vitamins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and calcium channel antagonists.

2.5. Baseline demographic and clinical characteristics

The following baseline information was obtained: patient age, patient gender, education level, disease course, HAMD score, HAMA score, Mini-Mental State Scale (MMSE) score (Tombaugh and McIntyre, 1992), Fazekas scale score for white matter lesions (Fazekas et al., 1987), and National Institutes of Health Stroke Scale (NIHSS) score (Brott et al., 1989).

2.6. Follow-up and evaluation of efficacy and adverse drug reactions

The patients were followed for 8 weeks. The following questionnaires were administered at baseline and at 1, 2, 4 and 8 weeks: 17-item HAMD (Hamilton, 1980), HAMA (Hamilton, 1959), Clinical Global Impression Scale (CGI) (Busner and Targum, 2007) and MMSE (Tombaugh and McIntyre, 1992). The primary outcome measures were the percentage reductions in the total HAMA and HAMD scores at 8 weeks compared with the respective baseline values. The proportions of patients in whom the treatment of depressive and anxiety symptoms was effective was also examined (defined as a $\geq 50\%$ reduction in the HAMD and HAMA scores vs. baseline, respectively, at 8 weeks). The secondary outcome measures were the absolute changes in the HAMA score, HAMD score, CGI severity scale (CGI-S) score, CGI improvement scale (CGI-I) score, CGI efficacy index (CGI-E) score and MMSE score at 1, 2, 4 and 8 weeks, in comparison to baseline. In addition, the proportions of patients achieving full remission of depressive symptoms

(defined as HAMD < 7 points) and anxiety symptoms (defined as HAMA < 8 points) at 8 weeks were compared between groups.

2.7. AEs

An adverse reaction form was provided to the patients to enable them to record any AEs in real time. Safety was also assessed using the following investigations: routine blood tests, serum electrolytes and biochemistry, routine urine tests, electrocardiogram and electroencephalogram. The Treatment Emergent Symptom Scale (TESS) score (National Institute of Mental Health (NIMH) 1985) was used to evaluate the severity of AEs: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = unsure.

2.8. Statistical analysis

SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. All data were tested for normality. The primary and secondary outcome measures were analyzed using the per-protocol set (patients who completed the treatment originally allocated). Normally distributed data are presented as the mean ± standard deviation and were compared within groups using the paired samples *t*-test and between groups using the independent samples *t*-test. Non-normally distributed data are presented as median (range) and were compared within and between groups using the Wilcoxon rank-sum test. AEs were analyzed using the intention-to-treat set (all patients randomized to receive one of the study interventions). AEs were compared between groups using the chi-squared test or Fisher's exact test. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Enrolment of the study participants

A flowchart summarizing patient enrolment is presented in Fig. 1. Among 157 patients screened for inclusion, 57 were excluded due to not meeting the enrolment criteria (n = 45), refusal to participate (n = 2) or other reasons (n = 10). Therefore, 100 patients were randomized to the tandospirone + escitalopram (n = 50) and escitalopram (n = 50) groups. Six patients in the tandospirone + escitalopram group discontinued the intervention during the 8-week study period due to admission to hospital for treatment of a comorbidity (n = 2) or poor adherence to therapy (n = 4). Five patients in the escitalopram group withdrew from the study due to poor adherence to therapy. Therefore, 44 patients in the tandospirone + escitalopram group and 45 patients in the escitalopram group completed the study.

3.2. Baseline characteristics of the study participants

The baseline demographic and clinical characteristics of the study participants are shown in Table 1. There were no significant differences between the two groups in age, gender, education level, disease course, or baseline HAMD, HAMA, MMSE, Fazekas scale or NIHSS scores (Table 1).

3.3. HAMD and HAMA scores

Comparisons of the HAMD and HAMA scores between groups are shown in Supplementary Table S1 and Fig. 2. The HAMD and HAMA scores decreased progressively in both the tandospirone + escitalopram group and escitalopram group, with significant reductions versus baseline observed at all time points (1, 2, 4 and 8 weeks) in both groups (Supplementary Table S1 and Fig. 2). Notably, the HAMD score and HAMA score were significantly lower in the tandospirone + escitalopram group than those in the escitalopram group at 1 and 2 weeks ($P < 0.001$) but not at 4 and 8 weeks (Supplementary Table S1 and Fig. 2).

The percentage reductions in HAMD score and HAMA score (relative to the respective baseline levels) are presented in Table 2 and Fig. 2. The percentage reductions in the HAMD score and HAMA score were significantly greater in the tandospirone + escitalopram group than those in the escitalopram group at 1 and 2 weeks ($P < 0.001$) but not at 4 and 8 weeks (Table 2).

3.4. Complete remission rates and effective treatment rates

The complete remission rates and effective treatment rates are listed in Table 3. The complete remission rates for depressive symptoms (i.e. proportion of patients achieving a HAMD score < 7 points) and anxiety symptoms (i.e. proportion of patients achieving a HAMA score < 8 points) increased progressively during the 8-week treatment period and were broadly similar between the two groups (Table 3). At 8 weeks, the complete remission rate for depressive symptoms was 38.6% and 44.4% in the tandospirone + escitalopram and escitalopram groups, respectively, and the corresponding values for anxiety symptoms were 43.2% and 44.4%, respectively.

The effective treatment rates for depressive symptoms and anxiety symptoms (i.e. the proportions of patients achieving a ≥50% reduction in HAMD and HAMA score, respectively) also increased progressively during the 8-week follow-up (Table 3). Notably, although the effective treatment rates for depressive and anxiety symptoms were comparable between groups at 4 and 8 weeks (exceeding 95% in both groups at 8 weeks), they were numerically greater in the tandospirone + escitalopram group than in the escitalopram group at 1 and 2 weeks (Table 3). Indeed, the effective treatment rates for depressive and anxiety symptoms at 2 weeks were 50.0% and 52.3%, respectively, in the tandospirone + escitalopram group but only 2.2% (for both) in the escitalopram group (Table 3).

3.5. Comparison of CGI scores

The CGI-S score exhibited a progressive decrease (indicating a reduction in illness severity) in both the tandospirone + escitalopram and escitalopram groups and was significantly lower than baseline at all time points (1, 2, 4 and 8 weeks) in both groups (Supplementary Table S1 and Fig. 3). The CGI-I score (which rates the change in clinical condition relative to baseline; a lower score means a greater improvement) also progressively decreased in both groups from 1 to 8 weeks (Supplementary Table S1 and Fig. 3). The CGI-E score, which is a measure of treatment efficacy, increased over time in both groups during the follow-up period (Supplementary Table S1 and Fig. 3). Notably, the improvements in the CGI-S, CGI-I and CGI-E scores were significantly greater in the tandospirone + escitalopram group than those in the escitalopram group at 1 and 2 weeks ($P < 0.01$ for all comparisons), but there were no significant differences at 4 or 8 weeks (Supplementary Table S1 and Fig. 3).

3.6. Comparison of MMSE scores before and after treatment in both groups

Compared with baseline, the MMSE score in the tandospirone + escitalopram group was significantly increased at 4 and 8 weeks ($P < 0.001$), but not at the earlier time points (Supplementary Table S1 and Fig. 4). By contrast, the MMSE score showed no significant changes in the escitalopram group (Supplementary Table S1 and Fig. 4). Furthermore, the MMSE scores were significantly higher in the tandospirone + escitalopram group than that in the escitalopram group at both 4 and 8 weeks ($P < 0.01$; Supplementary Table S1 and Fig. 4).

3.7. Comparison of adverse drug reactions

Two patients were hospitalized during the 8-week treatment period for conditions that were not related to their depressive and anxiety

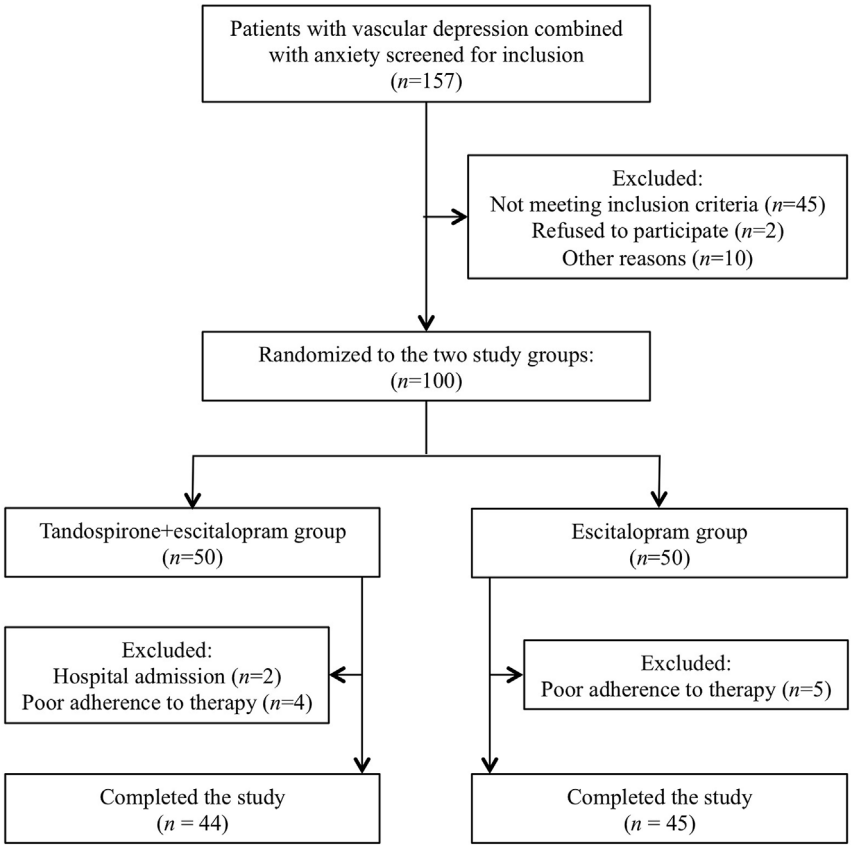

Fig. 1. Flowchart showing the process of patient enrolment.

conditions or their treatment. These two patients were excluded from the analysis because their comorbidity and its treatment can probably add further aggravate the depression and anxiety symptoms. The AEs were more commonly observed during the first 2 weeks of treatment (Table 4). The AEs were generally mild and tolerable and disappeared without the need for any specific treatment. The AEs in the tandospirone + escitalopram group (overall incidence of 18.0%) included nausea and abdominal distention (4 cases), dizziness, fatigue and drowsiness (4 cases) and constipation (1 case). The AEs in the escitalopram group (overall incidence of 16.0%) included nausea and abdominal distention (3 cases), dizziness and fatigue (3 cases), drowsiness (1 case) and constipation (1 case). In both groups, there were no obvious abnormalities in routine blood tests, serum electrolytes, serum biochemistry, routine urine tests, electrocardiogram or electroencephalogram, either before or after treatment.

4. Discussion

An important finding of the present study was that although HAMD and HAMA scores decreased progressively during the 8-week treatment period in both groups, they were lower in the tandospirone + escitalopram group than those in the escitalopram group at 1 and 2 weeks, but not at 4 and 8 weeks. Similarly, the improvements in CGI-S, CGI-I and CGI-E scores were greater in the tandospirone + escitalopram group than those in the escitalopram group at 1 and 2 weeks, but not at 4 and 8 weeks. However, MMSE scores were higher in the tandospirone + escitalopram group than those in the escitalopram group at 4 and 8 weeks. In addition, the incidences of AEs (which were all mild and tolerable) were comparable between groups. Only two SAEs were noted, and both were ruled out as being not related to the study drugs. Taken together, our findings suggest that augmentation of escitalopram with tandospirone results in a faster onset of anti-depressive and anxiolytic effects as well as a greater improvement in cognitive function.

Table 1
Baseline demographic and clinical characteristics of the study participants.

Characteristic	Tandospirone + escitalopram group (n = 44)	Escitalopram group (n = 45)	P-value
Age (years), mean ± SD	69.98 ± 4.44	70.93 ± 4.47	0.314
Gender, male/female	23/21	24/21	0.920
Education (years), mean ± SD	7.70 ± 2.53	8.27 ± 2.48	0.293
Disease course (months), mean ± SD	5.52 ± 1.86	5.31 ± 1.58	0.564
HAMD score, mean ± SD	29.45 ± 2.53	28.98 ± 2.30	0.355
HAMA score, mean ± SD	24.32 ± 2.67	24.00 ± 2.82	0.586
MMSE score, mean ± SD	20.75 ± 4.01	20.62 ± 4.06	0.882
Fazekas scale score, mean ± SD	2.32 ± 1.03	2.13 ± 1.10	0.415
NIHSS score, mean ± SD	2.27 ± 1.45	2.18 ± 1.39	0.753

HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; MMSE: Mini-Mental State Scale; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation.

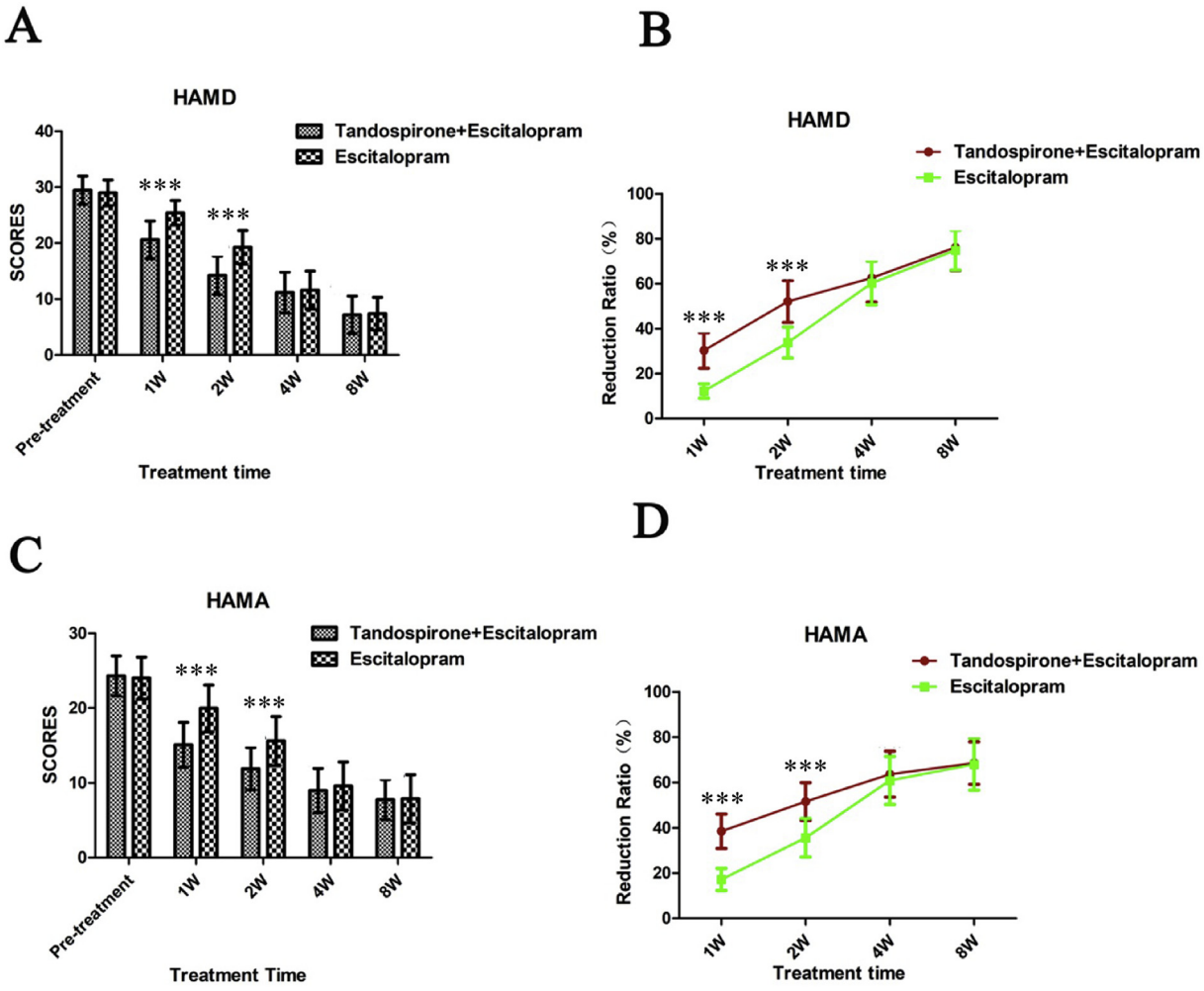

Fig. 2. Comparisons of HAMD score, HAMA score and percentage reductions in these scores at different time points between the two groups. A. Comparisons of HAMD scores at different time points: ***$P < 0.001$. B. Comparisons of the reductions in HAMD score at different time points: ***$P < 0.001$. C. Comparisons of HAMA scores at different time points: ***$P < 0.001$. D. Comparisons of the reductions in HAMA score at different time points: ***$P < 0.001$. The statistical comparisons were made using the independent samples *t*-test or independent samples Wilcoxon rank-sum test.

Table 2
Percentage reductions in the Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale versus baseline.

Scale	Time point	Tandospirone + escitalopram group ($n = 44$)	Escitalopram group ($n = 45$)	Difference (95%CI)	*P*-value[a]
HAMD score	1 week	30.31 ± 7.89%	12.26 ± 3.24%	15.48, 20.62	< 0.001
	2 weeks	52.08 ± 9.34%	33.82 ± 6.86%	14.81, 21.70	< 0.001
	4 weeks	62.61 ± 10.75%	60.31 ± 9.68%	−2.00, 6.61	0.290
	8 weeks	76.12 ± 10.20%	74.90 ± 8.85%	−2.80, 5.24	0.547
HAMA score	1 week	38.49 ± 7.61%	17.23 ± 4.86%	18.57, 23.94	< 0.001
	2 weeks	51.61 ± 8.37%	35.61 ± 8.51%	12.44, 19.56	< 0.001
	4 weeks	63.69 ± 10.09%	60.90 ± 10.61%	−1.57 , 7.16	0.207
	8 weeks	68.57 ± 9.37%	68.02 ± 11.40%	−3.85, 4.95	0.805

Data are presented as the mean ± standard deviation. HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale. ***$P < 0.001$ vs. baseline value in the same group.

[a] *P*-value for comparison between the tandospirone + escitalopram group and escitalopram group.

Classically, it is believed that antidepressants require 2–4 weeks to take effect (Machado-Vieira et al., 2008). However, in the present study, significant effects of escitalopram on HAMD, HAMA and CGI-S scores were observed after only 1 week. Furthermore, the beneficial effects of escitalopram increased progressively during the 8-week treatment period, indicating that up to 8 weeks was required for the effects of this antidepressant to fully develop in patients with vascular depression. These observations are consistent with previous reports that SSRIs begin to exert effects by the end of the first week of administration, with further progressive improvement during the next 6 weeks (Taylor et al., 2006). Indeed, there is some evidence that escitalopram may have a faster onset of action than other antidepressants (Gourion, 2008). Nonetheless, there is considerable interest in the development of therapeutic strategies with a faster rate of onset, as the earlier alleviation of symptoms would be of great benefit to patients (Ramaker and Dulawa, 2017). This may be of particular relevance to patients with vascular depression, who are usually elderly people who often have one or more somatic diseases and poor tolerance to drugs,

Table 3
Complete remission rates and effective treatment rates.

Scale	Time point	Tandospirone + escitalopram group (n = 44)	Escitalopram group (n = 45)
HAMD complete remission rate	1 week	0 (0.0%)	0 (0.0%)
	2 weeks	3 (6.8%)	0 (0.0%)
	4 weeks	5 (11.4%)	4 (8.9%)
	8 weeks	17 (38.6%)	20 (44.4%)
HAMA complete remission rate	1 week	1 (2.3%)	0 (0.0%)
	2 weeks	3 (6.8%)	1 (2.2%)
	4 weeks	12 (27.3%)	12 (26.7%)
	8 weeks	19 (43.2%)	20 (44.4%)
HAMD effective treatment rate	1 week	1 (2.3%)	0 (0.0%)
	2 weeks	22 (50.0%)	1 (2.2%)
	4 weeks	39 (88.6%)	40 (88.9%)
	8 weeks	44 (100%)	45 (100%)
HAMA effective treatment rate	1 week	1 (2.3%)	0 (0.0%)
	2 weeks	23 (52.3%)	1 (2.2%)
	4 weeks	39 (88.6%)	40 (88.9%)
	8 weeks	43 (97.7%)	43 (95.6%)

Data are presented as n (%). HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale.

which may impact on the effectiveness of antidepressant therapy.

Vascular depression is often accompanied by anxiety disorders. Tandospirone is a partial agonist at postsynaptic 5-HT1A serotonin receptors and a full agonist at 5-HT1A receptors in presynaptic membranes (Huang et al., 2017). It is thought that these actions of tandospirone inhibit the activity of the hippocampus and amygdala, which are believed to be involved in the induction of anxiety (Huang et al., 2017). Several clinical trials have shown that tandospirone is an effective and safe therapy for anxiety disorders (Huang et al., 2013; Tao et al., 2012; Nishitsuji et al., 2004). Additionally, tandospirone has been reported to reduce the severity of depressive symptoms in patients with dementia (Masuda et al., 2002). In the present study, the addition of tandospirone to escitalopram resulted in superior improvements in depressive symptoms (HAMD score), anxiety symptoms (HAMA score) and

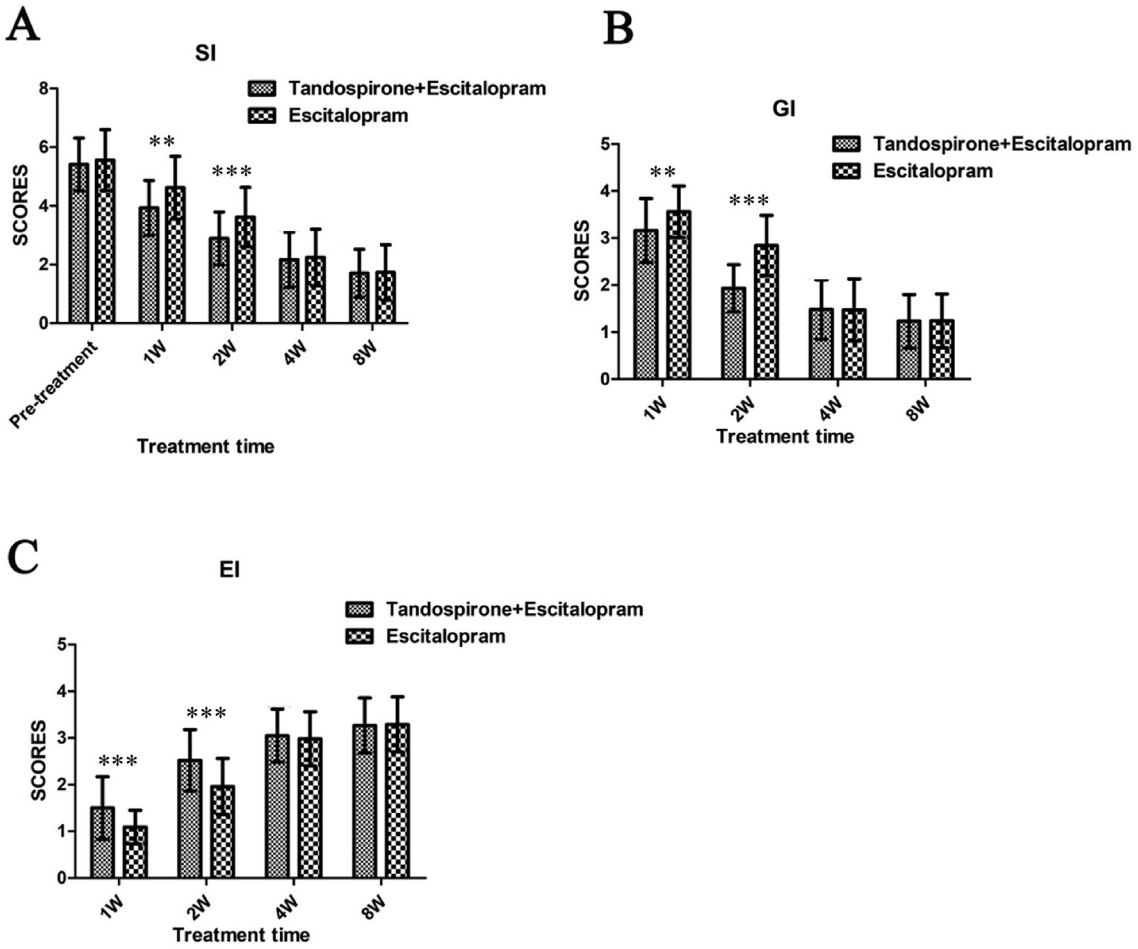

Fig. 3. Comparisons of CGI-S, CGI-I, and CGI-E scores at different time points between the two groups. A. Comparisons of CGI-S scores at different time points: $^{**}P < 0.01$, $^{***}P < 0.001$. B. Comparisons of CGI-I scores at different time points: $^{**}P < 0.01$, $^{***}P < 0.001$. C. Comparisons of CGI-E scores at different time points: $^{***}P < 0.001$. The statistical comparisons were made using the independent samples t-test or independent samples Wilcoxon rank-sum test.

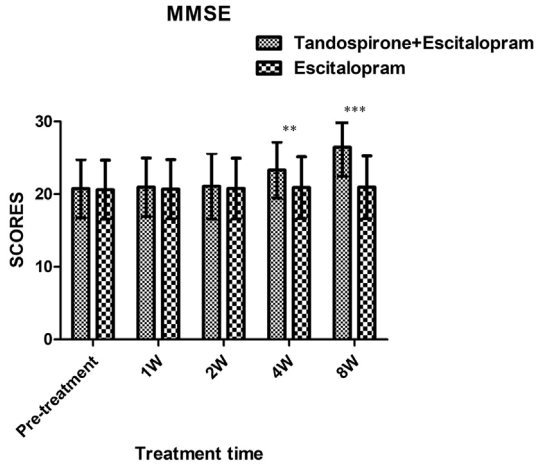

Fig. 4. Comparisons of MMSE scores at different time points between the two groups. $^{**}P < 0.01$, $^{***}P < 0.001$. The statistical comparisons were made using the independent samples *t*-test or independent samples Wilcoxon rank-sum test.

Table 4
Incidence of adverse events.

Time point	Tandospirone + escitalopram group ($n = 50$)	Escitalopram group ($n = 50$)
0–7 days	3 (6.0%)	3 (6.0%)
8–14 days	4 (8.0%)	3 (6.0%)
15–21 days	1 (2.0%)	1 (2.0%)
22–56 days	1 (2.0%)	1 (2.0%)
Total during 8-week follow-up	9 (18.0%)	8 (16.0%)

Data are presented as *n* (%).

psychiatric illness severity (CGI indexes) during the early phase of therapy (i.e. at 1 and 2 weeks). This is consistent with previous research indicating that tandospirone exerts a synergistic effect with antidepressants in the treatment of MDD (Lin et al., 2018). Although the effects of combination therapy on HAMD, HAMA and CGI scores were not superior to those of escitalopram monotherapy at 4 and 8 weeks, it should be emphasized that this does not detract from the important benefits of combination therapy observed in our study, namely an earlier onset of action and thus earlier relief of symptoms. Indeed, our results are in agreement with another study suggesting that tandospirone may speed up the onset of diazepam's action in patients with MDD (Yamada et al., 2003).

An additional finding of this study was that patients with vascular depression and anxiety had vascular cognitive impairment, as noted previously (Sachdev et al., 2014). Importantly, combination treatment with tandospirone and escitalopram improved cognitive functions at 4 and 8 weeks, whereas escitalopram monotherapy had no significant effect on MMSE score. This indicates that alleviation of cognitive dysfunction is an additional important advantage of augmenting escitalopram with tandospirone. Other published research has demonstrated a beneficial effect of tandospirone on cognitive function and memory (Sumiyoshi et al., 2001; Baba et al., 2015). A variety of mechanisms may underlie the effects of tandospirone on cognitive function in patients with vascular depression (Millan et al., 2012). We speculate that the mechanisms may involve: 1) 5-HTIA receptor-mediated increases in cortical and/or hippocampal dopaminergic and cholinergic neurotransmission; 2) enhancement of memory function; 3) preferential activation of presynaptic 5-HT1A autoreceptors, leading to reduced release of 5-HT from neurons; and 4) enhanced regeneration of hippocampal neurons (Yasuno et al., 2003; Mori et al., 2014). Interestingly, tandospirone has been reported to potentiate fluoxetine-induced increases in dopamine release in the rat medial frontal cortex via 5-HT1A receptors (Yoshino et al., 2002), and this mechanism may also have contributed to our observed effects of tandospirone on MMSE score because the medial frontal cortex has been implicated in decision making, learning and consolidation of memory (Euston et al., 2012). Horiguchi et al. showed that tandospirone reversed the cognitive impairment induced by phencyclidine in rats and that this effect was abolished when using a 5-HT1A antagonist; dopamine, GABA and the MAPK/ERK signaling pathway have been suggested to be involved in these effects (Horiguchi et al., 2016). Glutamatergic neurotransmission and lactate metabolism are also possibly associated with the effects of tandospirone on cognitive function through 5-HT1A receptors (Uehara et al., 2014). Nevertheless, the present study was not designed to explore the mechanisms of tandospirone in cognitive functions and further studies are needed to establish the mechanisms underlying the actions of tandospirone.

This study has some limitations. First, this was a single-center study with quite a small sample size, so the generalizability of the findings is not known. Second, the patients were not blinded to the intervention used. Third, a placebo (negative control) group was not included. Both escitalopram and tandospirone are well-known drugs that are superior to placebo and therefore have no placebo effect by themselves (Wade et al., 2002; Baldwin et al., 2016; Cipriani et al., 2009b; Takahashi et al., 2010). Fourth, the follow-up period was only 8 weeks, so it remains unknown whether augmentation of escitalopram with tandospirone would have any longer-term benefits. Fifth, whether tandospirone can augment the effects of any other antidepressant drugs was not studied.

In conclusion, augmentation of escitalopram with tandospirone may improve symptoms during the first 2 weeks of therapy and enhance cognitive function at 4–8 weeks in patients with vascular depression and anxiety. Thus, the combination of tandospirone with a SSRI may be a promising regimen for the treatment of vascular depression and anxiety. Multicenter randomized controlled trials are merited to establish whether tandospirone in combination with a SSRI should be a standard treatment for patients with vascular depression and anxiety.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.04.024.

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