Original Article

EEG power spectral analysis reveals tandospirone improves anxiety symptoms in patients with Alzheimer's disease: a prospective cohort study

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Background: To study the efficacy of tandospirone citrate in treating Alzheimer's disease (AD) patients with anxiety.

Methods: Thirty mild-to-moderate AD patients with anxiety symptoms were randomly divided into a monotherapy group (donepezil) and a combination therapy group (donepezil and tandospirone). The treatment lasted for 12 weeks. Drug efficacy was regularly assessed using psychological assessment scales and quantitative pharmaco-electroencephalogram (QPEEG) power spectral analysis.

Results: After 12 weeks of treatment, the mean Hamilton Anxiety Scale (HAMA) score and mean Neuropsychiatric Inventory (NPI) score of the combination therapy group were 5.13±4.18 and 4.2±5.0, respectively, which was significantly lower compared to baseline and the monotherapy group (all $P<0.05$). The mean attention score on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) was 0.07±0.26 for the combination group, which was significantly lower than that of the monotherapy group ($P<0.05$). QPEEG revealed that the power values of the δ wave in the right prefrontal lobe, left middle temporal lobe and right posterior temporal lobe decreased in the combination therapy group but not in the monotherapy group. Similarly, the power values of the α2 wave in the right parietal, right posterior temporal and left middle temporal lobes, and the β1 wave power values of left middle temporal and left posterior temporal lobes were also significantly decreased in the combination therapy group, but not in the monotherapy group.

Conclusions: Tandospirone citrate can significantly improve anxiety symptoms and attention in patients with mild to moderate AD. QPEEG examination might provide a objective way for the efficacy of the tandospirone in anxiety symptoms of the patients with Alzheimer's disease.

Keywords: Alzheimer's disease (AD); anxiety; tandospirone citrate; EEG power spectrum

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Introduction

Alzheimer's disease (AD) is a disease of the central nervous system (CNS) characterized by a progressive decline in cognitive function. More than 90% of cases belong to the sporadic variety of the disease. The main symptoms of AD are impaired cognitive function, decreased activities of daily life, and behavioral and psychological symptoms of dementia (BPSD) (1). It has been reported that at different stages of AD, more than 90% of patients will present different levels of BPSD, such as anxiety, depression, irritability, agitation, disinhibition, hallucinations, and delusions. Anxiety can occur in the early stage, peak at the moderate stage, and gradually subside in the severe stages of the disease due to apathy. It can also lead to depression, agitation, irritability, and other symptoms of BPSD (2), as well as exacerbate decline, reduce quality of life, increase the burden to caregivers, and increase financial burden (3). Currently, no drugs have been approved by the FDA for the treatment of BPSD. Donepezil is recommended for early Alzheimer's disease, but its effect on the symptoms of anxiety is not good.

5-hydroxytryptamine (5-HT) is an important neurotransmitter and neuromodulator involved in the decline of cognitive function and the occurrence of various BPSD symptoms in AD patients (4). It is derived from raphe nuclei of the brain and is widely distributed in the CNS, including regions such as the cerebral cortex, thalamus, hypothalamus, and basal ganglia. It includes 14 receptor subunits, among which, the density of the 5-HTR1A receptor decreases with age (approximately 10% every 10 years). The density of 5-HTR1A receptors in the hippocampus and dorsal raphe nuclei is correlated with cognitive impairment in AD patients (5). 5-HTR1A is an important neurotransmitter involved in the occurrence of neurosis and affective disorders such as anxiety and depression. Moreover, many clinical and preclinical studies have found that the 5-HTR1A receptor is involved in the occurrence of AD emotional symptoms which can complicate the course of the disease.

Tandospirone, a derivative of azapirone, is a partial agonist for the 5-HTR1A receptor. It has been approved for the treatment of Generalized anxiety disorder but also for anxiety symptoms caused by other CNS diseases, such as cognitive impairment and Parkinson's disease. Sato *et al.* used tandospirone to treat BPSD symptoms caused by AD and vascular dementia. After 8 weeks of treatment, scores on the Neuropsychiatric Inventory (NPI), including factors such as delusions, agitation, depression, anxiety, and irritability, were significantly improved (6). However, the study only included 13 patients, the research period was only 8 weeks, and there was no control group, which could not fully explain this result. Moreover, most of these clinical studies rely on the NPI scale when assessing the symptoms of BPSD, while the beneficial effect of tandospirone on cognitive function remains unknown. In addition, most studies use the NPI scale to evaluate the efficacy and rely on caregiver observations. There may be missing symptoms and biased descriptions, which are not accurate and objective.

Pharmaco-electroencephalography (PEEG) is a new quantitative analysis method that combines EEG quantitative technology with the pharmacological effects of CNS drugs, and investigates the correlation between them. It can also determine the plasma concentration at different times according to the pharmacokinetic and pharmacodynamic characteristics of the drug. At the same time, it can also use power spectrum analysis technology to quantitatively analyze changes in EEG background activity induced by the drugs at the corresponding time, thereby establishing different PEEG modes. It is an objective indicator that reflects changes in human brain function caused by medications. Therefore, performing quantitative electroencephalography (QEEG) on any drug that affects brain function can be regarded as an excellent electrophysiological detection method. PEEG was initially mainly used for psychopharmacological research. Currently, QPEEG is commonly used for elucidating the neurological effects of nootropic and anti-dementia drugs (7).

The following study compared the effects of the anti-anxiety medication tandospirone combined with donepezil and donepezil alone in the cognitive function and anti-anxiety of AD patients with anxiety. We also establish a QPEEG model so as to evaluate the effects timely of drugs in clinical practice, and optimize drug treatment programs. This method of quantification provides an objective basis for further clarification of the pathogenesis of AD and the mechanism of action of anti-anxiety drugs. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6647).

Methods

Demographic and clinical evaluation

AD patients who visited the Memory Outpatient Department, Zhejiang Provincial People's Hospital were included in this study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The

ethics committee of the hospital approved the protocol. Informed consent was obtained from the family members of the patients (spouse or children). Inclusion criteria were as follows: (I) aged 55–80 years, male or female, with vision, hearing, and health condition that enabled them to complete follow-up assessments. Patients were matched based on ethnicity, gender, age, and physical condition in order to minimize bias; (II) patients met the diagnostic criteria for AD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); (III) patients with mild to moderate AD and a mini-mental state examination (MMSE) score of 16–24 points; (IV) patients with anxiety symptoms, with a Hamilton Anxiety Scale (HAMA) score >8 points; (V) patients without depression symptoms, with a Hamilton Depression Scale (HAMD) score ≤7 points; (VI) brain CT or MRI examination confirming the diagnosis of AD; (VII) patients and their families or guardians signed informed consent.

Exclusion criteria were as follows: (I) patients with dementia caused by any other reason, such as frontotemporal lobar dementia, Frontal Assessment Battery (FAB) <12 points; (II) patients with high-signal lesions larger than 5 mm in diameter in the T2-FLAIR sequence of brain MRI; (III) patients with severe heart, lung, liver, kidney and hematopoietic system diseases; (IV) patients with any mental or nervous system diseases apart from AD; (V) patients with mental disorders caused by psychoactive substances; (VI) patients who have been involved in other clinical trials within the last 30 days; (VII) patients who had alcohol and drug dependence; (VIII) women who were breastfeeding, pregnant, or likely to become pregnant during the trial.

In this prospective cohort study, patients were randomly divided into the monotherapy group (donepezil hydrochloride) or combination therapy group (donepezil hydrochloride and tandospirone citrate tablets). The dosage of donepezil hydrochloride was 5–10 mg per day, and the tandospirone started from 2.5 mg/day and was increased on a weekly basis. The tandospirone citrate tablets were administered 3 times a day, 10 mg each time, to 3 times a day, 20 mg daily. The study lasted 12 weeks and was conducted between January 2017 and December 2018.

Calculation of sample size

As this was a pilot study, no formal calculation of sample size was performed. According to the physical condition of elderly patients (EEG examination takes 1 hour), we included 30 physically healthy AD patients and an elderly healthy control group to observe the practicability of the research program.

Assessment scales

The MMSE was used to assess general cognitive impairment, the HAMA was used to assess anxiety status, and the HAMD was used to assess depression status, all of which were considered the main indicators for enrollment at screening. The MMSE and HAMA were also used as evaluation indicators during follow-up. The NPI was used to assess BPSD, including symptoms of anxiety, depression, hallucinations, delusions, and agitation. The AD Assessment Scale-Cognitive section (ADAS-Cog) was used to assess cognitive function, including recall, naming, abstract thinking capability, orientation, attention, and language comprehension ability. The Fullerton Advanced Scale (FAB) scale was used to assess executive and motor functions related to the frontal lobe. Adverse events (AEs) were assessed with the Treatment Emergent Symptom Scale (TESS). Assessments were performed at baseline and at the 12th week (end of the study). In order to avoid subjective assessment, all scales are evaluated by professional psychological assessors who do not know the design.

EEG power assessment

According to the International Electrode Positioning Method of the 10/20 System, electrodes were placed on the scalp at the frontal, parietal, occipital and temporal areas of the patient's left and right brain hemispheres. Reference electrodes were placed on both ears, and ground electrodes were placed at any location. After the patient was at rest for 5 minutes, EEG signals were collected using a BM-116 digital EEG machine, sampling for 1 hour each time, at baseline and after 12 weeks of treatment in a quiet surrounding environment, suitable temperature, and dim light. The power percentage of each frequency band for each brain area was recorded including $\alpha,\beta,\delta,\theta$. The data collected above are all quantitative data, compared between the single-agent treatment group and the combination treatment group, and the baseline and post-treatment comparisons.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. All statistical tests were two-sided. The measurement data were expressed as mean ± standard deviation. Intragroup comparisons were performed using a paired

Table 1 Demographic characteristics and neuropsychological measures of the AD patients

Variable	Monotherapy	Combination therapy	Group comparison, P value (t)
N	13	16	NA
Age (years, mean ± SD)	71.15±10.7	74.68±9.53	0.36 (–0.94)
MMSE score (mean ± SD)	23.77±3.63	21.38±4.13	0.11 (1.64)
HAMA score (mean ± SD)	12.92±4.70	9.87±3.54	0.06 (1.99)
HAMD score (mean ± SD)	5.31±4.21	4.93±2.74	0.78 (0.28)
NPI score (mean ± SD)	6.92±6.29	9.69±6.75	0.27 (–1.13)
ADAS-Cog (mean ± SD)	11.03±7.71	9.74±5.12	0.59 (0.54)

AD, Alzheimer's disease; MMSE, mini-mental state examination; HAMA, Hamilton Anxiety Scale; NPI, neuropsychiatric inventory; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale.

t-test, and intergroup comparisons were performed using an independent sample *t*-test. P<0.05 was considered statistically significant. 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. If the patient only completes one examination or assessment, it will not be included in the statistical analysis.

Results

Demographic characteristics and clinical assessment data

A total of 30 patients were enrolled. One patient in the monotherapy group quit therapy due to a slow heart rate of <55 beats/min during treatment, and the remaining 29 patients were eligible and completed the full trial. There were 13 cases in the monotherapy group, and 16 cases in the combination group. There was no significant difference in age between the two groups. At baseline, the two groups did not show significant differences in the total scores of MMSE, HAMA, HAMD, NPI, and ADAS-Cog (P>0.05), and were comparable (details in *Table 1*).

Evaluation of therapeutic efficacy

After 12 weeks of treatment, the MMSE scores of the two groups increased compared to baseline, but the difference between the two groups was not significant (P>0.05). After 12 weeks of treatment, the HAM-A scores in the combination therapy group significantly decreased, and were significantly lower than the monotherapy group (P<0.05). After 12 weeks of treatment, the NPI scores of the two groups were significantly lower than the baseline value. The score of the tandospirone combined with donepezil treatment group was significantly lower than that of the donepezil group alone. The average NPI scores suggested that after 12 weeks of treatment, the BPSD of the combination therapy group significantly improved, and was better than that of the monotherapy group (P<0.05). The ADAS-Cog score showed no significant difference before or after treatment for both groups (P>0.05), while the attention score was significantly lower in the combination therapy group than in the monotherapy group after 12 weeks of treatment (P<0.05) (details in *Table 2*).

Adverse events of two groups

All adverse events are generally mild and tolerable, and most of them disappear within 2 weeks. Adverse events in the donepezil treatment group included nausea (3 cases), dizziness (3 cases), fatigue (1 case), and adverse events in the donepezil and tandospirone treatment group included nausea (2 cases), dizziness (4 cases), Diarrhea (2 cases). Other indicators including blood routine, urine routine, liver function, kidney function, electrocardiogram, etc. were not significantly different before and after treatment.

EEG power spectral analysis

After treatment, In the combined treatment group of donepezil and tandospirone, the most of relative power values of α, β, and δ all decreased significantly, which including the δ wave of the right prefrontal lobe, the α2 wave of the right parietal lobe, the δ wave, the α2 wave and the β1 wave of the left middle temporal, the β1 wave of left posterior temporal, the δ wave and the α2 wave of right posterior temporal(all P<0.05). However, there were no significant changes in the

Table 2 Neuropsychiatric assessment results after treatment with tandospirone in mild to moderate AD patients with anxiety

Treatment results (mean ± SD)	Monotherapy		Combination therapy	
	Before treatment	After treatment	Before treatment	After treatment
MMSE	23.77±3.63	24.55±3.88	21.38±4.13	23±4.84
HAMA	12.92±4.70	13.18±7.97	9.87±3.54	5.13±4.18*#
NPI	6.92±6.29	9.91±8.22	9.68±6.75	4.2±5.0*#
ADAS-Cog	11.03±7.71	9.95±4.22	9.74±5.12	8.62±3.46
Attention in ADAS-Cog	0.08±0.27	0.5±0.53	0.13±0.34	0.07±0.26*

*, there is a significant difference between the two groups after treatment, P<0.05; #, the score has a significant difference compared with that before treatment, P<0.05. AD, Alzheimer's disease; MMSE, mini-mental state examination; HAMA, Hamilton Anxiety Scale; NPI, neuropsychiatric inventory; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale.

Table 3 EEG power spectral analysis results in mild to moderate AD patients with anxiety

Brain area	Monotherapy		Combination therapy	
	Before treatment	After treatment	Before treatment	After treatment
FP2_δ	16.15±5.32	18.03±4.45	22.21±5.94	18.56±4.79*
P4_α2	10.45±4.34	10.35±3.60	13.18±3.83	11.74±2.51*
T3_δ	9.63±3.13	10.22±2.76	14.65±4.05	11.61±2.85*
T3_α2	6.36±2.18	6.25±0.92	7.31±1.61	6.14±1.00*
T3_β1	2.38±0.61	2.54±0.35	2.54±0.36	2.36±0.41*
T5_β1	2.45±0.88	2.73±0.52	2.91±0.49	2.46±0.61*
T6_δ	8.94±2.21	10.93±2.56*	12.44±3.62	11.13±3.26*
T6_α2	6.64±2.80	7.67±2.62	9.72±2.81	7.73±1.40*

*, comparisons before and after treatment were performed using a paired t-test, P<0.05. AD, Alzheimer's disease.

donepezil monotherapy group (details in *Table 3*).

Discussion

Tandospirone citrate, a 5-HTR1A partial receptor agonist, is widely used in the treatment of anxiety, depression, and other mental disorders (8). Anxiety is commonly experienced by AD patients (9), especially in mild to moderate AD patients. Given that the pathogenesis of AD includes alterations to the serotonergic system, there is a theoretical and clinical basis for using tandospirone citrate in the treatment of AD patients with anxiety symptoms.

Our results showed that for patients with mild to moderate AD accompanied by significant anxiety symptoms, tandospirone citrate significantly improved anxiety symptoms, BPSD, attention and cognitive function (10). In order to obtain an accurate assessment, we used the EEG power values to measure the therapeutic effect. The results showed that tandospirone citrate reduced the power values of the right prefrontal lobe, right parietal lobe, and bilateral temporal lobe, suggesting that QPEEG can be used as an objective indicator to evaluate drug efficacy in AD.

AD is the most common degenerative disease of the CNS that is accompanied by significant BPSD, including depression, anxiety, apathy, agitation, hallucinations, and delusions, of which anxiety and depression are the main symptoms in the early stages of AD. Donepezil hydrochloride and memantine hydrochloride are commonly used for the treatment of AD (11,12). In cases where AD is accompanied by significant BPSD, anti-anxiety drugs, antidepressants, and atypical antipsychotic drugs are recommended in combination with AD medication.

Previous studies have reported that binding of the 5-HTR1A receptor antagonist, WAY100635, in the

hippocampus and temporal cortex of AD patients significantly decreased (13). Recently, several 5-HTR1A receptor agonists have been suggested for the treatment of AD, however none of them have been clinically tested. In a follow-up study of 13 outpatients with AD or vascular dementia with BPSD (6), it was found that tandospirone could effectively improve BPSD, which was consistent with our findings. Previous studies have suggested that tandospirone can exert its anti-anxiety effect by activating 5-HT1A receptors and G proteins behind the synapse. On the one hand, tandospirone inhibits the activity of adenylate cyclase by coupling with G protein, which results in the reduction of cAMP, thereby inhibiting protein kinase A-mediated protein phosphorylation. On the other hand, tandospirone activates G protein-gated inwardly rectifying potassium channels by releasing Gβγ subunits, which leads to an outflow of intracellular K+, hyperpolarization of targeting neurons, and ultimately inhibits neuronal activity thus controlling anxiety (14).

5-HTR1A receptors are mainly distributed in the forebrain limbic system of the brain, such as the prefrontal lobe, temporal lobe, hippocampus, and raphe nuclei. These areas are also closely related to cognitive functions, such as memory, attention, and executive functions (15). Our results revealed that tandospirone had no effect on memory, but improved attention, which may be closely related to tandospirone increasing the density of 5-HTR1A receptors in these regions. Some studies have suggested that this is related to the 5-HTR1A receptor that is independently involved in the release of dopamine from the cerebral cortex. Clinical studies have found that the combination of tandospirone and atypical antipsychotic drugs can improve cognitive functions such as attention and executive function in patients with schizophrenia. To the best of our knowledge, the present study is the first to report that tandospirone improves attention in AD patients.

Studies have also found that the abnormal rate of EEG is higher in AD patients, which is manifested by the significantly increased power of low-frequency slow-wave θ and δ waves, and decreased power of the fast wave, especially in the frontotemporal area (16,17). Patients with mild to moderate AD also show atrophy of the frontal and temporal lobes (18) where a large number of 5-HTR1A receptors are located. Therefore, the administration of tandospirone citrate may increase the concentration of 5-HT in these regions, restore serotonin balance in the brain, promote the functioning of 5-HT neurons, ultimately improving the functioning of these cortices and reduce abnormal neuronal activity in AD patients. In our study, the slow wave relative power values (β wave and δ wave) of the frontal lobe and temporal lobe were significantly reduced after tandospirone treatment, and the relative power values of the alpha wave of the parietal and temporal lobe were also Decreased significantly. These results are in line with the theory that tandospirone improves frontotemporal lobe function in AD patients, suggesting that the detection of QPEEG can reflect the effect of tandospirone treatment and provide considerable evaluation indicators. However, the QPEEG test cannot provide an accurate cut-off value, and it cannot be used for accurate individual assessment. A larger sample size of data is required for verification.

In summary, tandospirone citrate can improve anxiety symptoms and attention in AD patients. Furthermore, the use of QPEEG could reflect the EEG changes after drug treatment. In subsequent research, we will increase the sample size, add the placebo group, prolong the observation period to observe the therapeutic effect of tandospirone citrate on other BPSD symptoms and cognitive functions, such as agitation, depression, executive function and speech, and regularly use QPEEG for continuous testing, so as to establish an assessment model with an accurate dose-response relationship.

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Footnote

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