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Original Article

Effects of escitalopram oxalate plus low-dose trazodone on psychological state and quality of life in patients with treatment-refractory depression

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Abstract: Objective: To analyze the effect of escitalopram oxalate (ESC) plus low-dose (LD) trazodone (TRA) on the psychological state and quality of life (QOL) of patients with treatment-refractory depression (TRD). Methods: In this retrospective study, we selected 111 TRD patients treated in the People's Hospital of Oedos Dongsheng District between February 2019 and February 2021; 54 patients who were treated with ESC were assigned to the control group (the Con) and the remaining 57 patients treated with ESC + LD-TRA were placed into the research group (the Res). The scores of Hamilton Anxiety/Depression Scale (HAMA, HAMD), Generic Quality of Life Inventory (GQOLI), Pittsburgh Sleep Quality Index Scale (PSQI), and Treatment Emergent Signs and Symptoms (TESS), as well as the levels of brain-derived neurotrophic factor (BDNF), S-100B protein (S-100B), and neuron-specific enolase (NSE) were determined before and after intervention. Besides, the curative effect and incidence of adverse reactions were compared. Furthermore, the risk factors affecting treatment ineffectiveness in TRD patients were analyzed by the multivariate Logistic model. Results: Evident reductions were observed in the Res in terms of HAMA, HAMD and PSQI scores and S-100B and NSE levels after intervention. Eight weeks after intervention, the TESS score was significantly reduced in the Res but not significantly different from the Con; while the scores of various dimensions of the GQOIL and the BDNF level were elevated markedly in the Res that were higher than those of the Con. Moreover, the Res presented with an evidently higher overall response rate than the Con. The two groups had no statistical significance in the overall incidence of adverse reactions (fever, irritability, insomnia, nausea, etc.). Based on the multivariate Logistic model analysis, HAMA, HAMD, PSQI, TESS, BDNF, S-100B, NSE, and treatment modality were not independent risk factors for treatment ineffectiveness in TRD patients. Conclusions: ESC + LD-TRA can significantly improve the psychological status, QOL, sleep quality and neurological function of patients with TRD while improving efficacy and ensuring patient safety.

Keywords: Escitalopram oxalate, low-dose trazodone, treatment-refractory depression, psychological state, quality of life

Introduction

Depression is a common psychiatric disorder that is characterized by dark mood, low self-evaluation and loss of interest in daily activities. For treatment-refractory depression (TRD), the symptoms will last longer, which will not only lead to a huge economic and living burden for patients, but also impose a heavy impact on social and medical care [1-3]. With uncharacterized etiology and pathogenesis, TRD is usually clinically treated by drug therapy and psychological intervention [4, 5]. Although medication has been indicated by previous clinical trials to be effective in controlling patients' conditions, there is no consensus on which drug regimen is preferred in clinical practice for TRD [6]. Therefore, the search for drug treatment schemes with higher efficacy is of great significance for the clinical management of TRD.

Reuptake inhibitors are currently widely used in the first-line clinical prescription of antidepressants, with the main choices including sero-

tonin and norepinephrine reuptake inhibitors versus selective serotonin reuptake inhibitors [7]. Escitalopram oxalate (ESC), a new selective serotonin reuptake inhibitor developed by a Swiss company [8], has a rapid onset of antidepressant activity compared to previous drugs [9]. However, as reported by some studies, ESC alone fails to achieve optimal treatment outcomes [10]. Thus, we are trying to improve the treatment of TRD by combining other agents. Trazodone (TRA) is an antidepressant with an innovative mechanism of action and a low risk of side effects [11]. Albertetal [12] also showed that a suitable dose of TRA, with the advantages of early onset and good tolerance, can become an effective antidepressant. Accordingly, we used low-dose (LD) TRA + ESC to treat TRD patients, and compared the effects of the combined medication with ESC monotherapy on patients' psychological state and quality of life (QOL), so as to verify the clinical advantages of the combined therapy and provide some references for such patients.

Data and methods

General information & enrollment criteria

We selected 111 TRD patients admitted between February 2019 and February 2021 and collected their clinical data for retrospective analysis, including 54 cases (control group, the Con) treated with ESC and 57 cases (research group, the Res) treated with ESC + LD-TRA. The mean age of the Con was (38.04±5.13) years, and the average course was (11.46±4.16) months. Patients in the Res were aged (39.19±5.37) years old on average with a disease course of (11.98±5.54) months. The two groups differed non-significantly in baseline data (P>0.05), with clinical comparability. All eligible patients, non-lactating women or non-substance abusers, met the diagnostic criteria of TRD, with intact clinical data and no related treatment within two months before enrollment. Cases were excluded based on the following criteria: other mental diseases; a history of allergy to research medications; serious heart, lung, kidney dysfunction and other diseases; malignant tumors. This research has been ethically ratified by the People's Hospital of Oedos Dongsheng District.

Treatment methods

The Con was treated with ESC (FB-200164, Nanjing Beiyu Biotech, China). Administration method: initially administered at 5 mg daily, the dose was increased to 10-20 mg daily according to the patient's response, for 8 weeks.

The Res was treated with ESC + LD-TRA (PF-04239, Beijing Pufei Biotech, China). ESC tablets were administered in the same way as the Con, and the TRA tablets were given at a dose of 25 mg per day for 8 weeks.

Analysis indexes

The Hamilton Anxiety and Depression Scale (HAMA, HAMD), Generic Quality of Life Inventory (GQOLI), brain-derived neurotrophic factor (BDNF), S-100B protein (S-100B), and neuron-specific enolase (NSE) were observed and recorded before and after treatment. The curative effect and incidence of adverse reactions (ARs) were counted.

(1) Psychological state. HAMA and HAMD scales, which were a 14-item tool with a score ranging from 0 to 56 and a 17-item instrument with a score range of 0-68, respectively, were used for anxiety and depression assessments. More severe anxiety and depression were indicated if the scores were higher.

(2) QOL. The QOL was assessed from the physical function, social function, mental function and material life using the GQOLI, with higher scores indicating better QOL.

(3) Pittsburgh Sleep Quality Index Scale (PSQI) and Treatment Emergent Signs and Symptoms (TESS). Patients' sleep quality was assessed before and after treatment using the PSQI, with scores inversely proportional to sleep quality. The severity of ARs were evaluated at 1 and 8 weeks after treatment using the TESS; the lower the score, the less severe the ARs.

(4) Neurological function. Five milliliters of fasting venous blood were collected before and one month after treatment in the early morning, and serum was collected via centrifugation to quantify BDNF, S-100B and NSE contents by enzyme-linked immunosorbent assay (ELISA). The operation steps are strictly in accordance with BDNF (XY0046A), S-100B (XY0316A) and NSE (XY0286A) ELISA kit (Shanghai Weiya Biotech, China) instructions.

(5) Therapeutic effects. The treatment effect was observed and recorded. Marked response means depressive symptoms disappeared with

Table 1. General information [n (%), mean ± SEM]

Factors	Control group (n=54)	Research group (n=57)	χ^2/t	P
Age (years old)	38.04±5.13	39.19±5.37	1.353	0.179
Course of disease (months)	11.46±4.16	11.98±5.54	0.557	0.579
Sex (male/female)	34/20	29/28	1.170	0.279
Body mass (kg)	59.31±13.58	58.07±16.09	0.438	0.663
Residence (rural/urban)	13/41	11/46	0.373	0.541
Marital status (married/single)	37/17	40/17	0.036	0.850

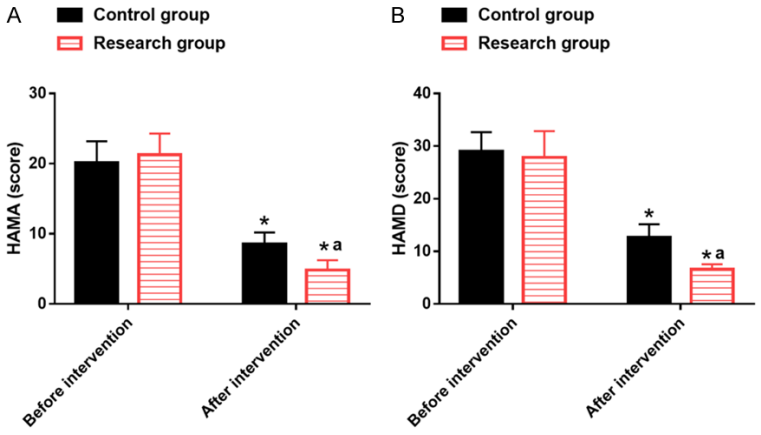

Figure 1. Impacts of escitalopram oxalate + low-dose trazodone on patients' psychological state. A. HAMA scores before and after intervention in both groups. B. HAMD scores before and after intervention in both groups. Note: * represents P<0.05 compared with the score before intervention; a represents P<0.05 compared with control group. HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale.

the ability to live and work normally. Response refers to relieved depressive symptoms and no serious social disorders. Non-response means inconformity with the above criteria. The overall response rate was the percentage of the sum of marked response and response patients in the total number of cases.

(6) Safety. The incidence of ARs was calculated after observing and recording the cases of fever, irritability, insomnia and nausea in the two groups.

Statistical processing

SPSS 22.0 was used for data processing in this study. Counting data (cases/percentage [n/%]) were analyzed by the χ^2 test between groups. Inter-group differences of measurement data were expressed by mean ± SEM via the t-test. Risk factors affecting treatment ineffectiveness in TRD patients were identified by multivariate Logistic model analysis. Statistical significance was indicated by P<0.05.

Results

General information

As can be found in **Table 1**, the general data such as age, course, sex, body weight, place of residence, and marital status were not statistically different between the Res and the Con (P>0.05).

Effect of ESC + LD-TRA on patients' psychological state

HAMA and HAMD scales were used to evaluate the anxiety and depression of TRD patients (**Figure 1**), so as to analyze the influence of two intervention methods on patients' psychological state. The analysis showed marked reductions in the two scores in both cohorts, with lower scores in the Res compared with the Con (P<0.05).

Influences of ESC + LD-TRA on patients' QOL

We employed the GQOLI scale to assess patients' QOL and found no significant inter-group difference before intervention (P>0.05); markedly elevated scores in physical function, social function, mental function and material life were found in both cohorts after intervention, with higher scores in the Res versus the Con (P<0.05; **Figure 2**).

Influences of ESC + LD-TRA on patients' sleep quality and severity of ARs

We analyzed the sleep quality and severity of ARs of the two groups using PSQI and TESS, respectively (**Figure 3**). The Res and Con dif-

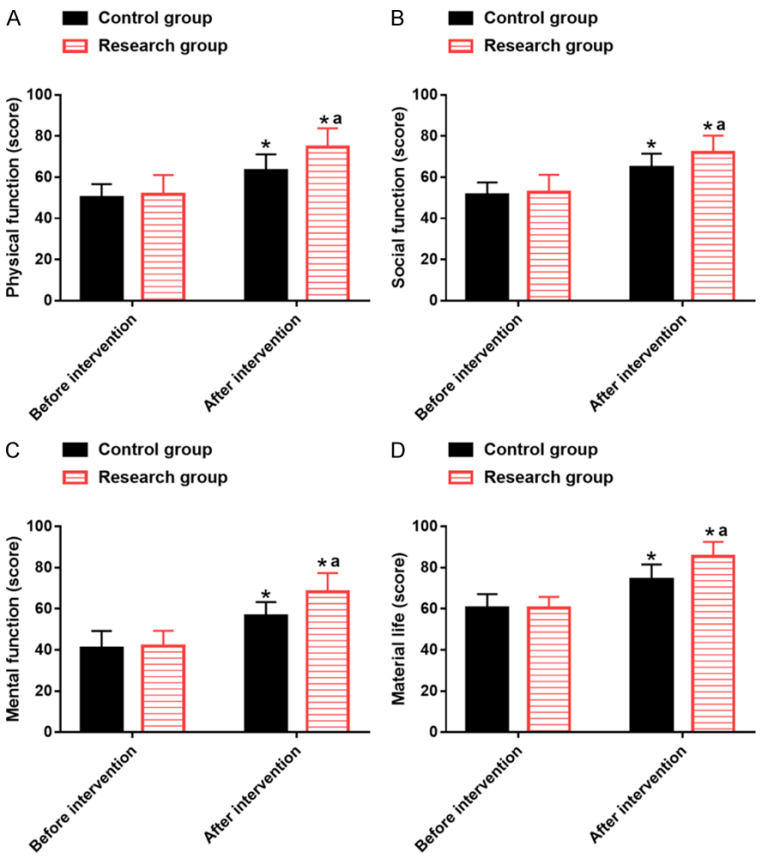

Figure 2. Influence of escitalopram oxalate + low-dose trazodone on patients' quality of life. A. Physical function scores of the two groups. B. Social function scores of the two groups. C. Mental function scores of the two groups. D. Material life scores of the two groups. Note: * represents P<0.05 compared with the score before intervention; a represents P<0.05 compared with control group.

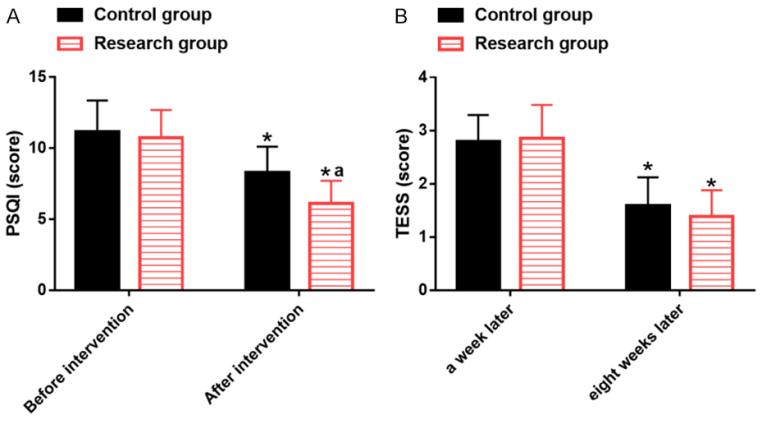

Figure 3. Influence of escitalopram oxalate + low-dose trazodone on patients' sleep quality (Pittsburgh Sleep Quality Index, PSQI) and severity of adverse reactions (Treatment Emergent Signs and Symptoms, TESS). A. PSQI scores of two groups before and after intervention. B. TESS scores of two groups at 1 and 8 weeks after treatment. Note: * represents P<0.05 compared with the score before intervention; a represents P<0.05 compared with control group. PSQI, Pittsburgh Sleep Quality Index Scale; TESS, Treatment Emergent Signs and Symptoms.

fered insignificantly in PSQI scores before intervention (P> 0.05); a marked decrease in PSQI scores was observed in both cohorts after intervention, with even lower scores in the Res (P<0.05). In terms of the TESS score, it was significantly lower in the Res at 8 weeks after treatment (P< 0.05) but was not significantly different from the Con (P> 0.05).

Impacts of ESC + LD-TRA on patients' neurological function

The levels of serum BDNF, S-100B and NSE were measured to evaluate patients' neurological function. As shown in **Figure 4**, the above three indexes showed similar levels in both groups before intervention (P>0.05), while BDNF increased statistically and S-100B and NSE reduced markedly after intervention (P< 0.05). In addition, higher BDNF and lower S-100B and NSE levels were determined in the Res (P<0.05).

Influence of ESC + LD-TRA on curative effects

By evaluating the curative effect of the two groups, it was found that the Res had an obviously higher total effective rate than the Con (89.47% vs. 68.52%, P<0.05), as presented in **Table 2**.

Impacts of ESC + LD-TRA on the incidence of ARs in patients

We observed and counted the incidence of ARs (fever, irritability, insomnia, and nausea) in the two groups (**Table 3**); the data showed no statistical significance in the overall inci-

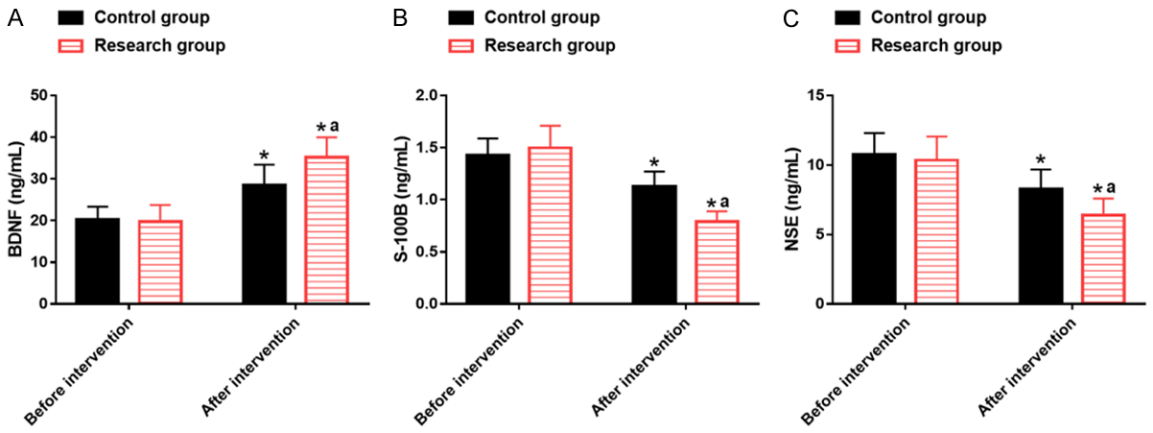

Figure 4. Impact of escitalopram oxalate + low-dose trazodone on patients' neurological function. A. BDNF before and after intervention in both groups. B. S-100B before and after intervention in both groups. C. NSE before and after intervention in both groups. Note: * represents P<0.05 compared with the level before intervention; a represents P<0.05 compared with control group. BDNF, Brain-Derived Neurotrophic Factor; S-100B, S-100B protein; NSE, Neuron-Specific Enolase.

Table 2. Impact of escitalopram oxalate + low-dose trazodone on curative effects [n (%)]

Categories	Control group (n=54)	Research group (n=57)	χ^2 value	*P* value
Response	19 (35.19)	23 (40.35)	-	-
Marked response	18 (33.33)	28 (49.12)	-	-
Non-response	17 (31.48)	6 (10.53)	-	-
Overall response rate	37 (68.52)	51 (89.47)	7.412	0.007

Table 3. Impact of escitalopram oxalate + low-dose trazodone on the incidence of adverse reactions in patients [n (%)]

Categories	Control group (n=54)	Research group (n=57)	χ^2 value	*P* value
Fever	4 (7.41)	1 (1.75)	-	-
Irritability	3 (5.56)	1 (1.75)	-	-
Insomnia	2 (3.70)	2 (3.51)	-	-
Nausea	3 (5.56)	2 (3.51)	-	-
Total incidence	12 (22.22)	6 (10.53)	2.792	0.095

dence of ARs between the Con and the Res (22.22% vs. 10.53%, P>0.05).

Risk factors affecting treatment ineffectiveness in TRD patients

Factors such as HAMA, HAMD, PSQI, TESS, BDNF, S-100B, NSE and treatment methods that had differences between groups were included in the analysis, and whether it affected the treatment ineffectiveness of TRD patients was taken as the dependent variable. As indicated by the multivariate analysis using the logistic regression model, none of the above factors were independent risk factors affecting treatment ineffectiveness in TRD patients (**Table 4**).

Discussion

Depression is recognized as the major cause of disability and a significant contributor to the global overall disease burden [13]. According to the statistics of the World Health Organization, an estimated 264 million people were affected by depression in 2020. The rising incidence of depression is accompanied by a high lifetime prevalence, with about 10.6% of patients experiencing TRD for life [14, 15]. Although various clinical antidepressants are confirmed to be

Table 4. Multivariate analysis of factors influencing treatment ineffectiveness in patients with treatment-refractory depression

Factors	β	S.E	Wald	P	OR	95% CI
HAMA	0.090	0.176	0.263	0.608	1.094	0.776-1.544
HAMD	0.112	0.114	0.972	0.324	1.119	0.895-1.397
PSQI	-0.136	0.150	0.824	0.364	0.873	0.651-1.171
TESS	-0.089	0.512	0.030	0.863	0.915	0.336-2.495
BDNF	0.010	0.059	0.026	0.871	1.010	0.899-1.133
S-100B	-0.464	2.220	0.044	0.834	0.629	0.008-48.772
NSE	0.240	0.193	1.542	0.214	1.272	0.870-1.858
Treatment modality	0.479	1.276	0.141	0.708	1.614	0.132-19.700

Hamilton Anxiety/Depression Scale (HAMA, HAMD), Generic Quality of Life Inventory (GQOLI), Pittsburgh Sleep Quality Index Scale (PSQI), Treatment Emergent Signs and Symptoms (TESS), brain-derived neurotrophic factor (BDNF), S-100B protein (S-100B), neuron-specific enolase (NSE).

effective in improving patient symptoms, no single antidepressant is universally effective for those with TRD [16]. Without well-controlled condition, the QOL of TRD patients and their families will inevitably deteriorate [17]. Therefore, it is necessary to explore combination therapies. This study focused on ESC + LD-TRA, with a view of improving the psychological state and QOL of such patients.

Patients' neurological function was assessed by detecting BDNF, S-100B and NSE levels in this study. BDNF has neurotrophic and neuroprotective effects, with evidence reporting marked lower plasma BDNF levels in TRD patients with suicidal tendency compared with those without [18]. In this trial, the elevation of BDNF level in the Res suggests that ESC + LD-TRA can reduce the suicidal tendency of TRD patients. On the other hand, significant increases in S-100B and NSE in depressive patients have been proved to be related to neuronal cell injury or degeneration [19, 20]. The more significant inhibition of their levels in the Res in this study suggests that the combination of drugs can greatly reduce the risk of neuronal injury in TRD patients. We also evaluated the psychological status of patients before and after intervention. The results identified greatly reduced anxiety and depression scores in both groups after intervention, with a far more significant reduction degree in the Res versus the Con, which indicated that the combined treatment was advantageous over the monotherapy in mitigating patients' anxiety and depression. From the analysis of curative effect, we can see that the total effective rate of treatment was notably higher in the Res, which is consistent with the above-mentioned research results on patients' psychological state and mutually validated. As far as patients' QOL was concerned, we comprehensively analyzed their physical function, social function, mental function and material life. The Res was found to have notably higher scores in all the four domains, indicating that ESC + LD-TRA can improve TRD patient' QOL more significantly than monotherapy. In another clinical study on the application of TRA in elderly depressed patients, TRA helps depressed patients to restore their QOL, similar to our research findings [21]. In addition to the QOL assessment, we evaluated the sleep quality of TRD patients. The results revealed a more significant reduction in the PSQI score in the Res after treatment, indicating that the combination of drugs is more effective in improving patients' sleep quality. In the Res, LD-TRA was added to the treatment regimen. In previous studies, TRA has been indicated to increase the duration of deep sleep in patients, which is associated with better sleep quality [22, 23]. In another study of antidepressants on sleep quality, TRA is shown to exert a sedative effect that rapidly improves sleep, consistent with our findings [24]. Finally, we compared and analyzed the differences in the occurrence of ARs. The data showed that the overall incidence of ARs in the Res was 10.53%, which was not significantly different from that in the Con, indicating that the combination of medication would not increase the risk of ARs in TRD patients. From the TESS scale, we found no statistical difference in the severity of ARs between the two groups at 1 and 8 weeks after treatment, con-

firming that the safety profile of the combination was comparable to ESC alone. In the past clinical trials, TRA showed better tolerance compared with other antidepressants. In this study, LD-TRA was used for combination administration, which greatly avoided the possible ARs caused by high plasma concentrations of TRA [25]. Finally, we conducted a multivariate analysis of the risk factors affecting the treatment ineffectiveness of patients, and found that factors such as HAMA, HAMD and treatment methods, which were different between the two groups, were not risk factors affecting treatment ineffectiveness in TRD patients. Hammen [26] proposed that cognitive dysfunction, stress, interpersonal relationship disorders and other factors were related to the ineffective treatment of refractory depression. However, these factors are not covered in this study. It is expected that in future studies, we will further explore and improve the risk factors affecting the ineffective treatment of TRD.

To sum up, for the treatment of TRD, ESC + LD-TRA outperforms ESC monotherapy, as it effectively improves patients' psychological state and neurological function and positively influences their QOL and sleep quality without increasing the risk of ARs, which is a medication protocol with both efficacy and safety benefits that deserves popularizing.

Disclosure of conflict of interest

None.

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