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ORIGINAL RESEARCH

Effect of Venlafaxine on Inflammatory Level in Patients with Depression

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Background: Venlafaxine is widely applied to treat depression. Herein, we further explore the effect of venlafaxine on inflammatory level in patients with depression.

Methods: Retrospectively, the medical data of patients (from January 2020 to February 2023, following up for 1 year) with depression (n=134) and without depression (health group, n=63) were collected. According to different treatment methods, patients with depression were categorized into the venlafaxine group (n=71) and the fluoxetine group (n=63). After treatment 8 weeks and 1 year, the baseline characteristics, therapeutic effect, inflammatory level and adverse events were analyzed.

Results: After treatment 8 weeks and 1 year, there were significant improvements about depression and inflammatory level in venlafaxine group and fluoxetine group ($P<0.05$), showing as the obvious decreases of Hamilton depression scale-17 (HAMD-17) score, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-4, IL-6 and neutrophil/lymphocyte ratio (NLR). Furthermore, the improvements of depression and inflammatory level were obvious in venlafaxine group than those of in fluoxetine group ($P<0.05$). There was no significant difference about adverse events between venlafaxine group and fluoxetine group.

Conclusion: In this study, venlafaxine use was associated with improvement in depressive symptoms and correlated with reduced levels of inflammatory markers in patients with depression.

Keywords: depression, venlafaxine, inflammatory level, therapeutic effect, Hamilton depression scale-17

Introduction

Depression, one of familiar mental diseases, is chiefly featured as the reduced interest, slow thinking, lacking initiative, pessimism, self-blame, bad diet and sleep.[1,2] At present, depression has become one of the global burden diseases. There is about 350 million people suffering from depression worldwide.[3] In recent years, the epidemiological survey shows that the incidence of depression among older individuals is on the rise, seriously affecting people's mental health and quality of life.[4] People with depression often worry that they have various diseases and feel unwell all over the body. In severe cases, depression patients may have suicidal thoughts and behaviors. It is commonly considered that the occurrence of depression can be reduced by early intervening.[5] What's more, various antidepressant drugs have been developed to mitigate depression, such as fluoxetine and venlafaxine.[6,7] Yet, it is still unclear the exact mechanism of venlafaxine on improving depression.

Reportedly, venlafaxine is the reuptake inhibitor for 5-hydroxytryptamine, serotonin, norepinephrine and dopamine.[8,9] As an antidepressant drug, venlafaxine has been reported that it can effectively improve depression in clinic.[10] Of note, several studies have pointed out that the antidepressant venlafaxine has an anti-inflammatory effect on many inflammatory diseases.[11–13] Moreover, current evidences have revealed that the inflammatory processes exert an important effect on the pathogenesis of depression.[14–16] A study on the traditional Chinese medicine "Chaihu - Bai Shao" also pointed out that its potential mechanism in treating post-stroke depression is closely related to the down-regulation of core inflammatory targets such as IL-6 and IL-1β.[17] The higher concentration of inflammation in depression patients is

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found in contrast to the healthy people.[18] This is robustly supported by meta-analyses of clinical data, which consistently demonstrate elevated levels of peripheral inflammatory markers, particularly C-reactive protein (CRP) and interleukin-6 (IL-6), in patients with depression compared to healthy controls.[19] Nevertheless, it is still unknown whether the treated effect of venlafaxine on depression is realized by reducing the inflammatory level.

Notably, different classes of antidepressants may possess distinct immunomodulatory properties. Studies have shown differences in inflammatory regulation between venlafaxine and paroxetine.[20,21] However, there are heterogeneity and contradictory results among different drugs and even similar drugs.[22] This provides a strong rationale for the choice of an active comparator. Therefore, our study employs fluoxetine as the active control, aiming to directly compare the potential differences between venlafaxine and fluoxetine in improving depressive symptoms and modulating inflammatory levels (eg, CRP, IL-6, TNF-α), thereby more precisely elucidating the mechanism of action of venlafaxine.

In this study, the medical records of patients with and without depression are collated. We carry out a retrospective study to assess the effects of venlafaxine on depressive symptom and inflammatory level, including CRP, IL-6, and TNF-α in patients with depression, which may provide a reference for the clinical prevention and treatment of depression.

Methods

Research Design

In this retrospective study, the medical data of each participant were collected. Written informed consent had been signed by each participant. This research was approved by the Ethical Committee of The Second Affiliated Hospital of Xi'an Jiaotong University (No. 2024 LS 080).

Participants

We collated the medical data of patients with depression (n=134) and without depression (as health group, n=63), from January 2020 to February 2023, following up for 1 year. According to the different treatment methods, patients with depression were categorized into the venlafaxine group (n=71) and the fluoxetine group (n=63). Treatment assignment was not randomized but was determined by the treating psychiatrist based on routine clinical practice. The choice of antidepressant was influenced by factors including, but not limited to, the patient's previous treatment history, tolerability profile, symptom severity, and presence of comorbid anxiety. Patients were required to remain on their initially assigned antidepressant monotherapy throughout the 1-year follow-up period. Inclusion criteria: (1) without taking any antidepressants before treatment 3 months; (2) no communication and understanding obstacles; (3) meeting the criteria of Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) 18 for a first episode or relapse of depression.[23] Exclusion criteria: (1) incomplete clinic information; (2) giving up treatment halfway and not taking medicine; (3) depression caused by serious illness; (4) with organic mental disorders. Thereafter, according to the existing case information, the changes of symptoms and the occurrence of adverse events during treatment period and follow-up period were systematically collated and analyzed.

Description of Treatment

According to patients' medical records, patients in the venlafaxine group were received the treatment of venlafaxine (75–150 mg/day, one time/day, Chengdu Kanghong Pharmaceutical, China) for 8 weeks, following up for 1 year. Patients in the fluoxetine group were received the treatment of fluoxetine (20–40 mg/day, one time/day, Lilly Suzhou Pharmaceutical, China) for 8 weeks, following up for 1 year.

Collection and Analysis of Clinical Data

Baseline Characteristics

The used baseline data were acquired from patients' medical records, including age, gender, body mass index (BMI), residence, marital status, average monthly household income, parents' education level, chronic disease, physical exercise, only child, solitude, smoke, drink and Montreal cognitive assessment (MoCA).

Therapeutic Effect

According to patients' medical records, the therapeutic effect was assessed by the Hamilton depression scale-17 (HAMD-17) score, which was used to evaluate depression at different time points. There were 17 items in HAMD-17 score. The score range of each item was from 0 to 4. Total HAMD-17 score≤7: normal. 8≤Total HAMD-17 score≤17: mild depression. About 18≤Total HAMD-17 score≤24: middle depression. Total HAMD-17 score≥25: severe depression. The higher HAMD-17 score meant more severe depression.[24]

Inflammatory Level

According to patients' medical records, the inflammatory indicators included C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-4, IL-6 and neutrophil/lymphocyte ratio (NLR), which were evaluated before treatment and after treatment 8 weeks and 1 year. Briefly, venous blood (4 mL) form each patient was collected on empty stomach at early morning. The NLR value in blood sample was assessed using the automatic blood cell analyzer (DP-H10, DyMind, China). In addition, after centrifuging blood samples, serum samples were collected. The levels of CRP, TNF-α, IL-1β, IL-4 and IL-6 in serum samples were severally evaluated using the human CRP assay kit (H126-1-2), TNF-α assay kit (H052-1-2), IL-1β assay kit (H002-1-2), IL-4 assay kit (H005-1-2) and IL-6 assay kit (H007-1-2), which were got from Nanjing Jiancheng Bioengineering (China). The detection was performed in accordance with manufacturer's manuals. Finally, the levels of these inflammatory indicators were evaluated by the microplate reader (VLBL0TD2, Thermo Fisher Scientific, USA).

Sample Size

According to early literature, the sample size was evaluated by the CRP level.[25] It was assumed that the CRP level was 0.88±1.07 before venlafaxine treatment, and the CRP level was 0.36±0.51 after venlafaxine treatment. Then, the sample size was calculated using PASS 15.0 software (NCSS Inc., USA). Parameters: power=90%; α=0.05; dropout rate=10%. In the end, the required sample size of each group was at least 63 cases. Therefore, it was effective for us to include 71 samples in venlafaxine group, 63 samples in fluoxetine group and 63 samples in health group.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0, with normality verified by Shapiro–Wilk test and homogeneity of variance confirmed by Levene test. The categorical variables were compared by χ^2 test. Data conforming to normal distribution are expressed as mean ± standard deviation. Independent sample *t* test was used for comparison between groups. Repeated measurement-ANOVA and Bonferroni test were applied for comparison at different time points in the same group. For variables that do not follow a normal distribution, the interquartile range M (P_{25}-P_{75}) is used to represent them. The significance level was bilateral $P<0.05$.

Results

Baseline Characteristics

As displayed in Table 1, the mean age of the venlafaxine group (n=71) was 30.45±5.74 years, the fluoxetine group (n=63) was 31.37±5.61 years and that of in the health group (n=63) was 29.49±4.66 years, which was non-significant difference ($P>0.05$). Besides, there were non-significant differences about gender, BMI, residence, marital status, average monthly household income, parents' education level, chronic disease, physical exercise, only child, solitude, smoke, drink and MoCA (Table 1, all $P>0.05$).

Evaluation of the Therapeutic Effect

According to the results of HAMD-17 score, there was non-significant difference between venlafaxine group and fluoxetine group before treatment (Table 2, $P>0.05$). Of note, the HAMD-17 score was significantly reduced after treatment 8 weeks or 1 year in venlafaxine group (Table 2, $P<0.05$). And the HAMD-17 score was significantly decreased after treatment 8 weeks or 1 year in fluoxetine group (Table 2, $P<0.05$). After treatment 8 weeks or 1 year, the decreasing trend of HAMD-17 score was more obvious in venlafaxine group than that of in fluoxetine group (Table 2, $P<0.05$).

Table 1 Comparison of Baseline Characteristics

Indicator		Venlafaxine (n=71)	Fluoxetine (n=63)	Health (n=63)	t/χ^2	*P*
Age (year)		30.45±5.74	31.37±5.61	29.49±4.66	−0.930	0.354
Gender [n (%)]	Male	38 (53.52)	35 (55.56)	33 (52.38)	0.056	0.813
	Female	33 (46.48)	28 (44.44)	30 (47.62)		
BMI (kg/m^2)		22.18±2.16	21.90±2.50	21.49±1.76	0.693	0.489
Residence [n (%)]	Village	24 (33.80)	20 (31.75)	22 (34.92)	0.064	0.800
	City	47 (66.20)	43 (68.25)	41 (65.08)		
Marital status [n (%)]	Married	32 (45.07)	25 (39.68)	27 (42.86)	0.396	0.529
	Unmarried	39 (54.93)	38 (60.32)	36 (57.14)		
Average monthly household income [n (%)]	<3000	30 (42.25)	26 (41.27)	24 (38.10)	0.076	0.963
	3000-5000	21 (29.58)	20 (31.75)	22 (34.92)		
	>5000	20 (28.17)	17 (26.98)	17 (26.98)		
Parents' education level [n (%)]	Primary/junior high School	5 (7.04)	4 (6.35)	4 (6.35)	1.462	0.481
	High school/technical secondary school	48 (67.61)	37 (58.73)	40 (63.49)		
	College/undergraduate	18 (25.35)	22 (34.92)	19 (30.16)		
Chronic disease [n (%)]	No	58 (81.69)	45 (71.43)	47 (74.60)	1.977	0.160
	Yes	13 (18.31)	18 (28.57)	16 (25.40)		
Somnipathy [n (%)]	No	45 (63.38)	38 (60.32)	40 (63.49)	0.133	0.716
	Yes	26 (36.62)	25 (39.68)	23 (36.51)		
Physical exercise [n (%)]	No	25 (35.21)	23 (36.51)	21 (33.33)	0.024	0.876
	Yes	46 (64.79)	40 (63.49)	42 (66.67)		
Only child [n (%)]	No	41 (57.75)	38 (60.32)	40 (63.49)	0.091	0.763
	Yes	30 (42.25)	25 (39.68)	23 (36.51)		
Solitude [n (%)]	No	11 (15.49)	10 (15.87)	7 (11.11)	0.004	0.952
	Yes	60 (84.51)	53 (84.13)	56 (88.89)		
Smoke [n (%)]	No	46 (64.79)	38 (60.32)	40 (63.49)	0.285	0.593
	Yes	25 (35.21)	25 (39.68)	23 (36.51)		
Drink [n (%)]	No	40 (56.34)	35 (55.56)	33 (52.38)	0.008	0.927
	Yes	31 (43.66)	28 (44.44)	30 (47.62)		
MoCA (score)		21.45±3.65	22.32±3.25	29 (28–30)	−1.444	0.151

Abbreviations: BMI, body mass index; MoCA, Montreal cognitive assessment.

Table 2 Comparison of HAMD-17 Score (Score)

Indicator	Time	Venlafaxine (n=71)	Fluoxetine (n=63)	Health (n=63)	*F*	*P*	Effect size (η^2)	95% *CI*
HAMD-17	Before treatment	22.46±4.60	22.44±4.20	3 (2–4)	0.001	0.979	0.000	−0.745–0.745
	After treatment 8 weeks	16.97±3.61*	20.32±3.86*	—	26.898	0.000	0.169	−0.517–0.855
	After treatment 1 year	9.35±3.26*	15.41±3.33*	—	112.904	0.000	0.461	−0.303–1.225

Notes: *$P<0.05$ vs Before treatment. $F_{time}=227.128$, $P_{time}=0.000$; $F_{interblock}=70.925$, $P_{interblock}=0.000$; $F_{interactive}=20.373$, $P_{interactive}=0.000$.
Abbreviation: HAMD-17, Hamilton depression scale-17.

Evaluation of the Inflammatory Level

The inflammatory factors included CRP, TNF-α, IL-1β, IL-4, IL-6 and NLR, which were non-significant difference between venlafaxine group and fluoxetine group before treatment (Table 3, all $P>0.05$). After treatment 8 weeks or 1 year, these inflammatory factors in venlafaxine group and fluoxetine group were obviously reduced compared with before treatment (Table 3, all $P<0.05$). Moreover, the decreases of CRP (8 weeks: 0.66±0.40 vs 0.83±0.60; 1 year: 0.44 ±0.24 vs 0.62±0.41), TNF-α (8 weeks: 33.49±18.09 vs 41.25±21.24; 1 year: 18.12±8.04 vs 24.58±10.30), IL-1β (8 weeks: 3.20±0.59 vs 4.00±0.49; 1 year: 1.79±0.28 vs 2.13±0.48), IL-4 (8 weeks: 1.97±0.30 vs 2.56±0.36; 1 year: 1.46±0.32 vs 2.06±0.42), IL-6 (8 weeks: 4.32±2.30 vs 5.23±2.48; 1 year: 3.48±1.10 vs 3.61±1.12) and NLR (8 weeks: 2.80±0.78 vs 3.08±0.65; 1 year: 1.86±0.54 vs 2.26±0.66) were more in venlafaxine group than those of in fluoxetine

Table 3 Comparison of Inflammatory Indicator

Indicator	Time	Venlafaxine (n=71)	Fluoxetine (n=63)	Health (n=63)	*F*	*P*	Effect size (η^2)	*95% CI*
CRP (mg/L)	Before treatment	1.06±0.84	1.08±0.81	0.39±0.21	0.018	0.894	0.000	−0.137–0.137
	After treatment 8 weeks	0.66±0.40*	0.83±0.60*	—	3.936	0.049	0.029	−0.049–0.107
	After treatment 1 year	0.44±0.24*	0.62±0.41*	—	9.752	0.002	0.069	0.010–0.128
TNF-α (pg/mL)	Before treatment	49.75±21.03	49.07±21.64	16.15±7.11	0.034	0.853	0.000	−3.587–3.587
	After treatment 8 weeks	33.49±18.09*	41.25±21.24*	—	5.210	0.024	0.038	−3.333–3.409
	After treatment 1 year	18.12±8.04*	24.58±10.30*	—	16.559	0.000	0.111	−1.535–1.757
IL-1β (pg/mL)	Before treatment	4.50±0.65	4.54±0.68	1.58±0.35	0.119	0.731	0.001	−0.117–0.119
	After treatment 8 weeks	3.20±0.59*	4.00±0.49*	—	71.105	0.000	0.350	0.272–0.468
	After treatment 1 year	1.79±0.28*	2.13±0.48*	—	25.187	0.000	0.160	0.082–0.278
IL-4 (pg/mL)	Before treatment	3.31±0.38	3.35±0.34	1.40±0.34	0.404	0.526	0.003	−0.056–0.062
	After treatment 8 weeks	1.97±0.30*	2.56±0.36*	—	105.653	0.000	0.445	0.367–0.523
	After treatment 1 year	1.46±0.32*	2.06±0.42*	—	87.044	0.000	0.397	0.319–0.475
IL-6 (pg/mL)	Before treatment	6.72±3.16	6.86±3.42	4.30±2.15	0.067	0.797	0.001	−0.548–0.550
	After treatment 8 weeks	4.98±2.59*	6.07±3.52*	—	4.262	0.041	0.031	−0.498–0.560
	After treatment 1 year	4.32±2.30*	5.23±2.48*	—	4.891	0.029	0.036	−0.376–0.448
NLR	Before treatment	3.48±1.10	3.61±1.12	1.70±0.41	0.446	0.505	0.003	−0.193–0.199
	After treatment 8 weeks	2.80±0.78*	3.08±0.65*	—	5.178	0.024	0.038	−0.080–0.156
	After treatment 1 year	1.86±0.54*	2.26±0.66*	—	15.147	0.000	0.103	0.005–0.201

Note: *P<0.05 vs Before treatment. CRP: F_{time}=29.302, P_{time}=0.000; $F_{interblock}$=2.562, $P_{interblock}$=0.112; $F_{interactive}$=1.611, $P_{interactive}$=0.204. TNF-α: F_{time}=127.528, P_{time}=0.000; $F_{interblock}$=3.398, $P_{interblock}$=0.068; $F_{interactive}$=6.014, $P_{interactive}$=0.003. IL-1β: F_{time}=946.942, P_{time}=0.000; $F_{interblock}$=30.603, $P_{interblock}$=0.000; $F_{interactive}$=126.030, $P_{interactive}$=0.000. IL-4: F_{time}=1789.113, P_{time}=0.000; $F_{interblock}$=85.396, $P_{interblock}$=0.000; $F_{interactive}$=109.385, $P_{interactive}$=0.000. IL-6: F_{time}=101.556, P_{time}=0.000; $F_{interblock}$=2.722, $P_{interblock}$=0.101; $F_{interactive}$=13.439, $P_{interactive}$=0.000. NLR: F_{time}=100.399, P_{time}=0.000; $F_{interblock[ii]}$=7.370, $P_{interblock}$=0.014; $F_{interactive}$=1.212, $P_{interactive}$=0.301.
Abbreviations: CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL, interleukin; NLR, neutrophil/lymphocyte ratio.

group after treatment 8 weeks or 1 year (Table 3, all P<0.05). Furthermore, after adjusting for covariates, a linear mixed-effects model was employed to analyze HAMD-17 scores and inflammatory markers. The analysis revealed statistically significant differences (Table 4, all P<0.05).

Adverse Events

The adverse events after treatment 8 weeks and 1 year were evaluated in venlafaxine group and fluoxetine group. After treatment 8 weeks, the adverse events in venlafaxine group mainly included dizzy (1 case), headache (1 case) and constipation (1 case), and in fluoxetine group included dizzy (1 case), drowsiness (1 case), thirst (1 case) and nausea (1 case) (Table 5). After treatment 1 year, the adverse event in venlafaxine group mainly included constipation (1 case), and in fluoxetine group included thirst (1 case) and constipation (1 case) (Table 5). There was non-significant difference between venlafaxine group and fluoxetine group about these adverse events after treatment 8 weeks or 1 year (Table 5, all P>0.05).

Table 4 Linear Mixed-Effects Model Analysis of Inflammatory Markers Across Groups: Adjusted for Covariates

Indicator	Effect size (η^2)	*95% CI*	*P*
HAMD-17	17.734	4.879–30.589	0.027
CRP	0.777	0.090–1.464	0.040
TNF-α	35.908	0.685–71.131	0.048
IL-1β	3.349	0.123–6.574	0.047
IL-4	2.439	0.423–4.454	0.035
IL-6	5.675	3.115–8.235	0.011
NLR	2.838	0.977–4.700	0.022

Table 5 Comparison of the Adverse Event [n (%)]

Indicator	Adverse event	Venlafaxine (n=71)	Fluoxetine (n=63)	χ^2	*P*
After treatment 8 weeks	Dizzy	1 (1.41)	1 (1.59)		
	Headache	1 (1.41)	0 (0.00)		
	Insomnia	0 (0.00)	0 (0.00)		
	Drowsiness	0 (0.00)	1 (1.59)		
	Blurred vision	0 (0.00)	0 (0.00)		
	Thirst	0 (0.00)	1 (1.59)		
	Nausea	0 (0.00)	1 (1.59)		
	Anorexia	0 (0.00)	0 (0.00)		
	Constipation	1 (1.41)	0 (0.00)		
Total		3 (4.23)	4 (6.35)	0.026	0.581
After treatment 1 year	Dizzy	0 (0.00)	0 (0.00)		
	Headache	0 (0.00)	0 (0.00)		
	Insomnia	0 (0.00)	0 (0.00)		
	Drowsiness	0 (0.00)	0 (0.00)		
	Blurred vision	0 (0.00)	0 (0.00)		
	Thirst	0 (0.00)	1 (1.59)		
	Nausea	0 (0.00)	0 (0.00)		
	Anorexia	0 (0.00)	0 (0.00)		
	Constipation	1 (1.41)	1 (1.59)		
Total		1 (1.41)	2 (3.18)	0.011	0.917

Discussion

As early reported, venlafaxine has been applied to treat depression in clinic.[26,27] In present study, out data further yield that venlafaxine has an effective function on improving depression, which may exert this effect by suppressing the inflammatory level in patients with depression.

There is a classic method to assess the depression status, that is, HAMD-17 score.[28] After antidepressant treatment, the reduction of HAMD-17 score represents the improvement of depression.[29] Therefore, we assess the depression status at different time points. Our data show that the HAMD-17 score is obviously reduced after treatment 8 weeks or 1 year in both venlafaxine group and fluoxetine group compared to baseline level (before treatment). This comparison provides novel clinical support for the differential immunomodulatory profiles of these two drug classes. This finding is consistent with early report that venlafaxine has a good effect on alleviating depression.[10,26] What's more, a key report has pointed out that venlafaxine has a potential advantage of antidepressant function and lesser adverse event profile in contrast to the fluoxetine-treated depression patients.[26] Similarly, our outcomes support these findings. However, these results should be regarded as generative and hypothetical, and need to be confirmed in larger-scale, multi-center trials. While we demonstrate a superior anti-inflammatory effect of venlafaxine over fluoxetine, we did not include a direct comparison with a established anti-inflammatory intervention (eg, NSAIDs or cytokine inhibitors). Future studies incorporating such a comparator are needed to fully contextualize the anti-inflammatory potency of antidepressants and to explore potential synergistic effects.

At present, most scholars believe that depression is mainly caused by the abnormal changes of monoamine transmitters in the brain (such as dopamine, 5-hydroxytryptamine and norepinephrine) and dysfunction of receptors, which can lead to the low mental activity and psychological function of patients as a whole.[30–32] Moreover, recent research illustrates that the inflammatory factors can affect monoamine neurotransmitter metabolism and hypothalamic-pituitary-adrenal axis to involve in the emotional regulation, which plays a certain role in the occurrence and development of depression.[33] The inflammatory factors can be produced by microglia and astrocytes in the brain, and can be produced by peripheral cells, which can enter the central nervous system in many ways to activate immune response. The inflammatory factors can also regulate the transmission of monoamine neurotransmitters in the nervous system, so it is considered that inflammatory factors are involved in the pathogenesis of depression.[33–36] Of note, existing study has

described that venlafaxine has an anti-inflammatory activity by suppressing the pro-inflammatory factors, such as CRP, TNF-α and IL-6.[12,25] Nevertheless, it is still unclear whether the antidepressant effect of venlafaxine is realized by inhibiting the inflammatory level. Consistent with early report,[37] our data reveal that venlafaxine can obviously reduce the inflammatory level in patients with depression, and this effect is more significant in venlafaxine group than fluoxetine group. These findings testify the above speculation. While both venlafaxine and fluoxetine have been associated with reductions in peripheral inflammatory markers, it is important to note that the findings have been mixed across clinical studies.

The clinical significance of the reduced inflammation is twofold. Firstly, it aligns with the superior improvement in depressive symptoms, suggesting a biologically relevant effect. Secondly, lower levels of CRP and IL-6 are linked to a reduced risk of somatic health complications, which is a critical treatment goal in a population with elevated comorbid physical health risks. The clinical relevance of these changes is underscored by their concurrent association with greater improvements in depressive symptoms in the venlafaxine group compared to the fluoxetine group. This parallelism suggests that the modulation of inflammation may be one pathway through which venlafaxine exerts its antidepressant effect, even if the absolute change in a single biomarker is not large, but this does not exclude its direct effect on other parallel or downstream effects such as the monoamine system.

Limitations

Here are several limitations should be noted. Firstly, the non-randomized design risks selection bias, measurement bias (especially for subjective endpoints), and residual confounding from unmeasured factors (eg, genetics, lifestyle), despite adjustments for known confounders. Secondly, the inherent constraints of the retrospective design, which preclude causal inference, and the modest effect sizes observed for the anti-inflammatory effects, which warrant further investigation. Finally, our assessment of adverse events relied on spontaneous reporting rather than systematic proactive questioning. Consequently, the reported incidence of adverse events, which was unusually low for both venlafaxine and fluoxetine, very likely represents a significant underestimation of the true burden. In the future, prospective, randomized, and blinded studies will be needed, and standardized adverse event monitoring should be adopted to confirm our findings.

Conclusions

All in all, our data display that venlafaxine has an effective function on improving depression, which may exert this effect by reducing the inflammatory level, manifesting as the decreases of CRP, TNF-α, IL-1β, IL-4, IL-6 and NLR. This not only strengthens the inflammatory hypothesis of depression but also raises the intriguing clinical possibility that baseline inflammatory status could someday inform the selection of antidepressants for individual patients. What's more, in the study, people treated with venlafaxine showed greater improvements in mood symptoms and inflammation markers compared to people treated with fluoxetine. Although these between-group differences were modest and require cautious interpretation, they consistently point toward a potential distinction between these treatments. This shows a possibility of a connection between inflammation and antidepressant effects, but future randomized controlled trials (RCTs) are needed to confirm.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The ethical review of this study is strictly enforced in accordance with the declaration of Helsinki. The studies involving human participants were reviewed and approved by the Ethical Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (No. 2024 LS 080). The patients/participants provided their written informed consent to participate in this study.

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Disclosure

The authors declare that they have no competing interests in this work.

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