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ORIGINAL ARTICLE

Bupropion Associated Immunomodulatory Effects on Peripheral Cytokines in Male with Major Depressive Disorder

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Background: Experimental and clinical studies have reported increased levels of pro-inflammatory cytokines in patients with major depressive disorder (MDD), suggesting that immune system dysregulation may contribute to MDD pathophysiology. **Aim:** Due to the lack of knowledge about the immune potential of antidepressants, this study investigated the immunomodulatory effects of bupropion, a norepinephrine–dopamine reuptake inhibitor. **Methods:** This study involved 18 patients with MDD treated with bupropion (150 mg/d) for 4 weeks and 23 healthy volunteers. All participants underwent multiplex bead-based cytokine assessment before and after bupropion treatment to quantify the following cytokines: interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, interferon-γ, tumor necrosis factor-α, granulocyte colony-stimulating factor, granulocyte-macrophage CSF, monocyte chemotactic protein-1, and macrophage inflammatory protein-1β. **Results:** Four-week treatment with bupropion significantly increased the levels of IL-1β (P = 0.011), IL-4 (P = 0.019), IL-5 (P = 0.019), IL-7 (P = 0.021), and IL-8 (P = 0.023) compared to the control group. Furthermore, the percentage change in most cytokines, including anti-inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13, was significantly increased after bupropion treatment. **Conclusion:** The promoted synthesis of anti-inflammatory cytokines to surpass the pro-inflammatory cytokines may be a crucial step in the treatment of MDD patients with bupropion.

Key words: Bupropion, cytokine, depression, inflammation, mood disorder

INTRODUCTION

Major depressive disorder (MDD) is a common serious psychiatric disorder, the pathophysiology of which may be impacted by immune system dysregulation.[1,2] In psychiatric immunology, innate immune cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, have key effects on neuroplasticity, neurotransmission, oxidative stress, and neuroendocrinological functions associated with the development of depression.[3] Previous studies also showed that individuals with MDD had higher peripheral concentrations of cytokines and chemokines, including IL-10, IL-12, IL-13, IL-18, soluble IL-2 receptor, IL-1 receptor antagonist, soluble TNF receptor 2, C-reactive protein, and monocyte chemotactic protein-1 (MCP-1).[2,3]

Cytokines can be classified as pro-inflammatory, such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-12, IL-17, IL-18, TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF), or anti-inflammatory including IL-4, IL-5, IL-10, IL-13, and transforming growth factor-β.[4-6] Pro-inflammatory cytokines stimulate the secretion of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, activate the hypothalamic–

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pituitary–adrenal (HPA) axis, and promote the secretion of the adrenocorticotropic hormone and glucocorticoids.[4] In chronic stress, the balance between the pro- and anti-inflammatory cytokines is disrupted leading to an imbalance between neurodegeneration and neuroprotection. Importantly, neurodegeneration in brain regions such as the hippocampus and frontal lobe can result in cognitive and memory impairments in depressed people,[4] leading to an overproduction of CRH and dysregulated glucocorticoid secretion. Furthermore, some pro-inflammatory cytokines, such as IL-1β and TNF-α, can stimulate the expression of serotonin reuptake transporters.[4,7] IL-1β and IFN-γ also stimulate indoleamine-2,3-dioxygenase, which, in turn, catalyzes the conversion of tryptophan into kynurenine to inhibit serotonin (5-HT) synthesis in the brain. These cytokines change the metabolism of monoamine neurotransmitters and cause depression.[4,7] Several studies have reported that antidepressants can significantly impact the balance between pro- and anti-inflammatory cytokines, although the available data are inconsistent regarding specific cytokines and the medications used.[2,8]

To date, no clinical studies have evaluated the potential association between bupropion, a norepinephrine–dopamine reuptake inhibitor, and cytokine modulation in MDD. A previous study in mice showed significantly reduced levels of IL-1β, TNF, and IFN-γ and higher levels of IL-10 after bupropion treatment.[9] Based on these preclinical findings, the present study was designed to examine the effects of bupropion on cytokine alterations in patients with clinical depression. A total of 17 cytokines were evaluated and compared between healthy controls and depressed patients before and after bupropion treatment.

MATERIALS AND METHODS

Participants

Individuals who voluntarily sought treatment for depression at the Beitou Branch of Tri-Service General Hospital in Taiwan between January 2012 and December 2012 and met the study inclusion criteria were eligible to participate. The protocol was approved by the Institutional Review Board for the Protection of Human Subjects at Tri-Service General Hospital (TSGH IRB 2-102-05-090). All participants were fully capable of comprehending the study purpose, procedures, risks, and discomforts, as well as the potential benefits associated with their participation. Written informed consent was obtained in accordance with the National Health and Medical Research Council guidelines, and participants were free to withdraw their participation at any time.

Eighteen hospitalized men diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition were recruited from the acute ward. The control group consisted of 23 physically and psychiatrically healthy male volunteers who did not receive bupropion. The severity of the depressive symptoms was assessed by the 17-item Hamilton Depression Rating Scale (HDRS).[10] All participants were over 20 years of age and were drug naive. Individuals were excluded if they met the criteria for substance-related use disorders or had a clinical history of other specific medical comorbidities, such as cardiovascular disease, diabetes, or rheumatic disease. Females were not included as cytokine levels can be influenced by the menstrual cycle, menopause, and the use of hormonal contraceptives or estrogens, which could introduce potential confounding factors.[11] In addition, patients whose depressive symptoms first manifested after the age of 40 years were also excluded since late-onset depression has been associated with elevated inflammation.

Cytokine assessment

Peripheral venous blood samples were collected in the morning between 8 and 9 am by venipuncture after fasting. Methodological techniques such as sampling, processing, and storage conditions can substantially increase the variability of cytokine measurements;[12] therefore, consistent procedures were followed for the collection, preparation, freezing, and thawing of all the serum samples, including the collection and handling of commercial samples. Cytokine levels were measured at baseline and after 4-week bupropion treatment.

The detection of soluble cytokines was performed using multiplex bead array assays as previously reported.[13] Briefly, 10 mL of peripheral blood was drawn into a Vacutainer gel and clot activator tube and then centrifuged to separate the serum, which was then aliquoted into NUNC-cryovial tubes and stored in a −84°C freezer. None of the serum samples had been thawed before use in the Luminex assay to simultaneously evaluate 17 cytokines. Luminex is a suspension assay that combines standard sandwich immunoassay principles with flow cytometry, allowing the multiplex analysis of up to 100 individual cytokines in a single microtiter plate well.[14-16] The Bio-Plex Pro Human Cytokine 17-plex Assay (M50-00031YV; Bio-Rad, Hercules, CA, USA) was used according to the manufacturer's instructions to analyze serum samples in the Bio-Plex 200 analyzer (Bio-Rad). The surveyed cytokines included IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte CSF (G-CSF), GM-CSF, IFN-γ, MCP-1, macrophage inflammatory protein (MIP)-1β, and TNF-α. Standard curves were created from duplicate values, and all samples were analyzed as single determinations. All analyses were performed in one batch using kits from the same production lot.

Statistical analysis

Clinical demographics, changes in HDRS, and pre- and posttreatment cytokine levels in the MDD and control groups were compared using paired samples *t*-tests. Baseline and posttreatment cytokine levels in both the groups were tested using one-way ANOVA, and the association between treatment response and cytokine levels was examined using repeated-measures ANOVA. Descriptive statistics are presented as the mean ± standard deviation. All statistical analyses were conducted using the Statistical Package for the Social Sciences software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 41 patients were screened and underwent postbaseline evaluation for cytokine alteration. The 4-week treatment was completed without discontinuation in the depression group which received 150 mg/day of bupropion. Demographic characteristics, including height and weight, in the patients at baseline were similar between the two groups, and the mean body mass index was 23 kg/m² [Table 1].

The mean total HDRS scores at baseline were higher in the depression group than in the control group (13.56 vs. 0.35), whereas the levels of the cytokines IL-4 (P = 0.043), IL-5 (P = 0.032), IL-7 (P = 0.04), and IFN-γ (P = 0.035) were significantly lower in the depression group. There was no significant difference in the concentrations of IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, MCP-1, MIP-1β, and TNF-α in depressed subjects compared with control subjects [Table 1].

At posttreatment, the mean total scores of HDRS response were 3.61 points in the depression group and 0 points in the control group (P = 0.00). The cytokine comparison within the depression group after 4 weeks of treatment revealed significantly increased levels of IL-4 (P = 0.015), IL-7 (P = 0.044), and IFN-γ (P = 0.012), whereas MCP-1 significantly decreased (P = 0.047) [Table 2 and Figure 1].

The mean change from baseline in the total HDRS score posttreatment was −9.95 points in the depression group and −0.35 points in the control group. The between-group mean change from baseline in the levels of IL-1β, IL-4, IL-5, IL-7, and IL-8 after treatment in the depression group and control group were 0.26 pg/mL and-0.77 pg/mL (mean difference, 1.03 points; P = 0.011), 1.051 pg/mL and −0.711 pg/mL (mean difference, 1.76 points; P = 0.019), 0.756 pg/mL and −1.015 pg/mL (mean difference, 1.77 points; P = 0.019), 2.407 pg/mL and −5.002 pg/mL (mean difference, 7.4 points; P = 0.021), and 3.584 pg/mL and −3.137 pg/mL (mean difference, 6.72 points; P = 0.023) [Figure 2 and Supplementary Table 1].

Table 1: Clinical demographics and comparison of baseline cytokine levels in 18 patients with depression and 23 healthy controls*

Demographics	Depression (n=18)	Controls (n=23)	P†
Age (years)	23.94±2.94	28.17±3.39	**0.000**
Height (cm)	170.61±5.31	171.22±5.51	0.724
Weight (kg)	65.99±8.1	68.52±8.75	0.349
BMI (kg/m²)	22.7±2.9	23.32±2.17	0.439
HDRS	13.56±5.95	0.35±0.93	**0.000**
Cytokine‡			
IL-1β	2.23±2.34	2.05±1.04	0.398
IL-2	13.41±12.62	7.25±8.58	0.356
IL-4	2.59±1.89	3.51±1.61	**0.043**
IL-5	3.04±2.17	4.17±2	**0.032**
IL-6	11.55±14.06	10.15±4.99	0.579
IL-7	5.35±5.08	10.59±14.79	**0.040**
IL-8	13.72±10.45	15.03±5.5	0.171
IL-10	36.76±66.05	34.55±44.9	0.846
IL-12	46.63±67.99	40.78±42.04	0.992
IL-13	2.59±3.14	2.28±1.3	0.367
IL-17	13.76±12.75	16.79±11.63	0.125
G-CSF	29.73±33.64	25.17±9.63	0.605
GM-CSF	30.45±26.49	7.56±9.21	0.858
IFN-γ	162.61±114.62	238.48±109.81	**0.035**
MCP1	64.44±93.63	12.87±3.93	0.246
MIP1b	55.64±29.57	41.15±10.09	0.125
TNF-α	18.83±30.11	12.86±7.43	0.815

*Data are presented as mean±SD, †Significant effects were marked with bold characters (P<0.05), ‡Unit for cytokine was pg/mL. G-CSF=Granulocyte colony-stimulating factor; GM-CSF=Granulocyte-macrophage colony-stimulating factor; HDRS=Hamilton Depression Rating Scale; IFN=Interferon; IL=Interleukin; MCP=Monocyte chemotactic protein; MIP=Macrophage inflammatory protein; SD=Standard deviation; TNF=Tumor necrosis factor; BMI=Body mass index

The differences in the percentage change in cytokine ratios between the groups are shown in Table 3 and Figure 3. Interestingly, the percentage change for most cytokines significantly increased after bupropion treatment (P < 0.05), except for IL-2 (P = 0.797), suggesting that the promotion of the synthesis of anti-inflammatory cytokines to surpass the pro-inflammatory cytokines may be a crucial step in the treatment of patients with bupropion.

DISCUSSION

To the best of our knowledge, this is the first study to confirm that the therapeutic range of bupropion can induce both pro-inflammatory and anti-inflammatory effects in patients

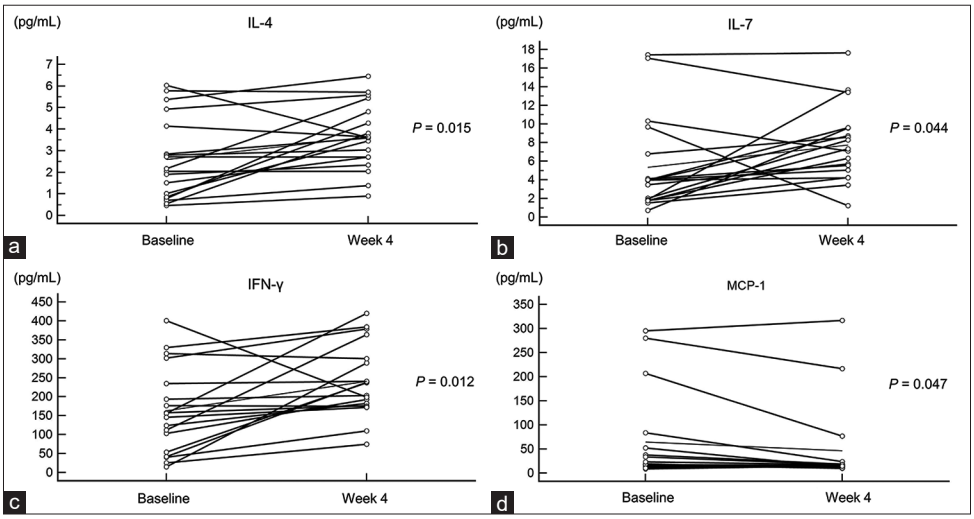

Figure 1: Representative graphs showing cytokine levels before and after treatment of bupropion. Comparison of the plasma levels of (a) IL-4, (b) IL-7, (c) IFN-γ, and (d) MCP-1. *IFN = Interferon, IL = Interleukin, MCP = Monocyte chemotactic protein

Table 2: Changes in serum inflammatory cytokine levels in different treatment groups

Cytokine*	Depression group, mean±SD			Control group, mean±SD		
	Baseline	Week 4	*P*	Baseline	Week 4	*P*
HDRS	13.56±5.95	3.61±3.6	**0.000**	0.30±0.93	0.00±0.00	0.088
IL-1β	2.23±2.34	2.49±2.47	0.459	2.05±1.04	1.28±0.91	**0.001**
IL-2	13.41±12.62	12.97±17.16	0.834	7.25±8.58	5.68±6.45	0.172
IL-4	2.59±1.89	3.64±1.54	**0.015**	3.51±1.61	2.8±1.49	0.067
IL-5	3.04±2.17	3.8±1.95	0.186	4.17±2.00	3.16±1.51	**0.017**
IL-6	11.55±14.06	13.04±13.93	0.429	10.15±4.99	7.76±4.67	0.054
IL-7	5.35±5.08	7.76±4.04	**0.044**	10.59±14.79	5.59±2.49	0.115
IL-8	13.72±10.45	17.31±12.3	0.072	15.03±5.5	11.89±5.98	**0.026**
IL-10	36.76±66.05	33.22±41.27	0.606	34.55±44.9	25.85±39.62	**0.026**
IL-12	46.63±67.99	37.52±37.58	0.335	40.78±42.04	32.11±52.22	0.064
IL-13	2.59±3.14	5.39±10.95	0.224	2.28±1.30	1.95±1.35	0.109
IL-17	13.76±12.75	15.89±12.84	0.35	16.79±11.63	12.76±12.78	0.074
G-CSF	29.73±33.64	33.63±31.26	0.245	25.17±9.63	21.17±11.31	0.084
GM-CSF	30.45±26.49	29.74±36.4	0.344	7.56±9.21	8.22±7.85	0.788
IFN-γ	162.61±114.62	241.06±96.93	**0.012**	238.48±109.81	203.65±124.31	0.196
MCP-1	64.44±93.63	46.36±83.38	**0.047**	12.87±3.93	14.05±6.63	0.423
MIP-1β	55.64±29.57	45.54±13.81	0.093	41.15±10.09	45.38±22.12	0.358
TNF-α	18.83±30.11	18.06±23.85	0.825	12.86±7.43	8.80±5.76	**0.01**

*Unit for cytokine was pg/mL. Significant effects were marked with bold characters ($P<0.05$). G-CSF=Granulocyte colony-stimulating factor; GM-CSF=Granulocyte-macrophage colony-stimulating factor; HDRS=Hamilton Depression Rating Scale; IFN=Interferon; IL=Interleukin; MCP=Monocyte chemotactic protein; MIP=Macrophage inflammatory protein; SD=Standard deviation; TNF=Tumor necrosis factor

with MDD. The 4-week treatment of depressive patients with bupropion resulted in a greater increase from baseline in IL-1β, IL-4, IL-5, IL-7, and IL-8 than the control group accompanied by a reduction in the HDRS scores. The plasma levels of several cytokines, including IL-4, IL-5, IL-7, and IFN-γ, were not significantly different between the groups despite lower concentrations in patients with depression than in healthy volunteers at baseline. Furthermore, the percentage change in most cytokines, including anti-inflammatory cytokines IL-4, IL-5, IL-10, and IL-13, was significantly increased after

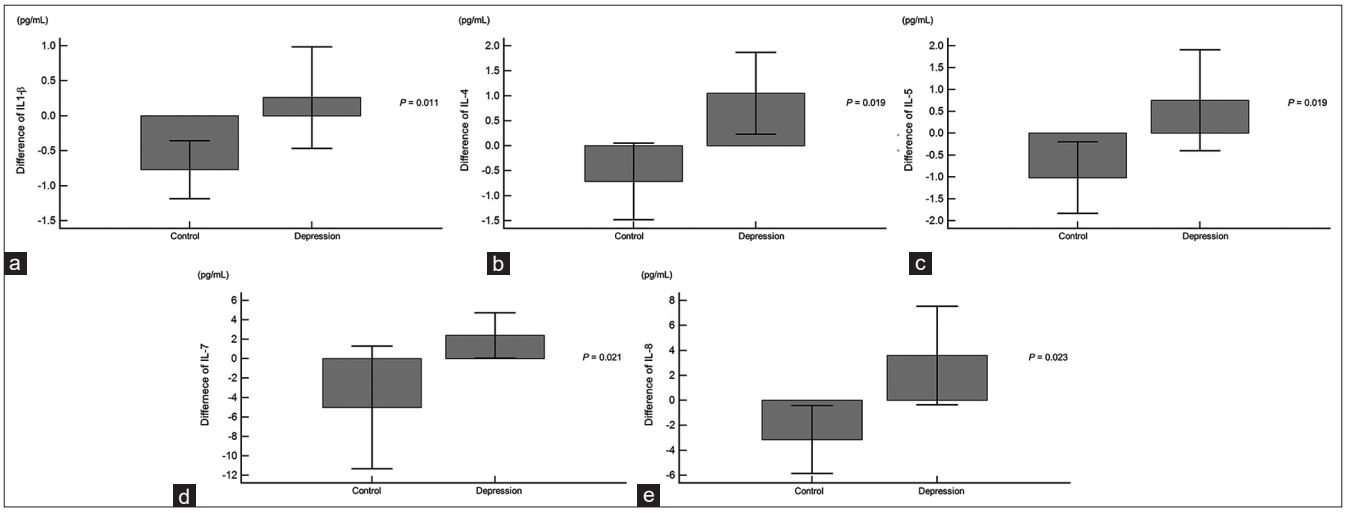

Figure 2: Comparison of the serum levels of (a) IL-1β, (b) IL-4, (c) IL-5, (d) IL-7, and (e) IL-8 between the two groups. **P* < 0.05 Data are shown as a mean ± standard deviation. IL = Interleukin

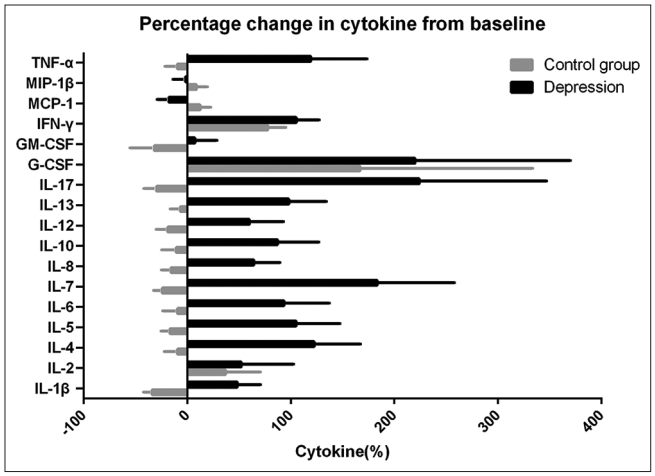

Figure 3: Percentage change from baseline in cytokine levels after 4 weeks. * Data are shown as a mean ± standard error of the mean. IL = Interleukin, TNF = Tumor necrosis factor, MCP = Monocyte chemotactic protein, IFN = Interferon, MIP = Macrophage inflammatory protein, G-CSF = Granulocyte colony-stimulating factor, GM-CSF = Granulocyte-macrophage colony-stimulating factor

bupropion treatment. That is, the anti-inflammatory response overwhelms the inflammation effect. These findings suggest that patients have an activated immune system during the disease and undergo immune rebalance during treatment. The outcome highlights the current state of this field and provides guidance for future studies.

Cytokines are secreted by monocytes or lymphocytes, as well as brain cells including neurons, endothelial cells, astrocytes, and microglia. They may play a role in the pathophysiology of depression by affecting the metabolism of monoamines such as dopamine, norepinephrine, and serotonin.[7] Pro-inflammatory cytokines can induce sickness behaviors (e.g., fatigue and sleepiness) and symptoms of anxiety or depression,[17] as well as activate the HPA axis, which in turn inhibits immune function.[4] Elevated peripheral pro-inflammatory markers in depressed individuals are correlated with the severity of depression and even the number of previous depressive episodes.[18-20] In this study, IL-1β, IL-2, IL-6, IL-12, and TNF-α were slightly higher in the MDD group compared to healthy volunteers, although the difference was not statistically significant. However, IL-7 and IFN-γ were lower in depression patients. Previous data indicate that the extent of cytokine variations is positively correlated with the illness duration and inversely correlated with the age at disease onset.[17,20] In this MDD cohort, the illness duration ranged from 0.5 to 91 weeks, suggesting that significant changes in the cytokine landscape may require a longer disease duration. Nevertheless, the onset of depression at a young age may have contributed to the lower levels of IL-7 and IFN-γ. Nonetheless, the phenotypic heterogeneity of MDD should be taken into consideration, as elevated HPA axis activity was reported in melancholic depression, whereas higher levels of pro-inflammatory markers have been described in atypical depression.[2]

Low levels of the anti-inflammatory cytokines IL-4 and IL-5 were observed in the depression group in agreement with the current knowledge that depression is associated with increased levels of circulating pro-inflammatory cytokines but reduced levels of anti-inflammatory cytokines.[4] However, in chronic stress, immune cells remain unaffected, which may be due to the hypersecretion of pro-inflammatory cytokines that causes glucocorticoid secretion and disrupts the normal functions of receptors, leading to glucocorticoid resistance.[21] Studies have reported that IL-4, IL-10, and IL-13 were

Table 3: Percentage change in the serum inflammatory cytokine level from baseline

Cytokine	Mean±SD (%)	95% CI		*P**
		Lower limit	Upper limit	
IL-1				
Control	−33.96±39.72	−51.14	−16.78	**0.001**
Depression	48.32±94.13	1.51	95.13	
IL-2				
Control	36.82±161.25	−32.91	106.55	**0.797**
Depression	51.98±214.71	−54.79	158.75	
IL-4				
Control	−9.38±61.45	−35.95	17.19	**0.003**
Depression	122.49±189.78	28.12	216.87	
IL-5				
Control	−16.71±40.51	−34.23	0.81	**0.003**
Depression	105.04±179.82	15.62	194.46	
IL-6				
Control	−9.40±67.60	−38.63	19.84	**0.018**
Depression	93.23±185.10	1.18	185.28	
IL-7				
Control	−24.15±40.15	−41.51	−6.79	**0.003**
Depression	183.27±315.97	26.14	340.40	
IL-8				
Control	−15.71±43.34	−34.46	3.03	**0.002**
Depression	64.25±106.41	11.33	117.17	
IL-10				
Control	−10.62±67.02	−39.60	18.37	**0.016**
Depression	86.99±170.01	2.44	171.54	
IL-12				
Control	−18.85±52.20	−41.43	3.72	**0.017**
Depression	59.85±139.77	−9.66	129.35	
IL-13				
Control	−6.57±47.19	−26.97	13.84	**0.004**
Depression	98.00±153.29	21.77	174.24	
IL-17				
Control	−29.63±58.28	−54.84	−4.43	**0.025**
Depression	224.03±521.04	−35.08	483.13	
TNF-α				
Control	−19.19±57.12	−43.88	5.51	**0.008**
Depression	119.25±229.32	5.22	233.29	

*Significant effects were marked with bold characters (P<0.05). CI=Confidence interval; IL=Interleukin; SD=Standard deviation; TNF=Tumor necrosis factor

significantly higher, promoted by chronic HPA hyperactivation in depressed patients before administration of antidepressants than in healthy controls, with a concomitant decrease in IL-2 and IFN-γ due to reduced capture of 5-HT.[21-23] The illness duration in our cohort was 23.02 ± 28.08 weeks, indicative of an acute-to-subacute depression phase, which may have contributed to the inability to detect a chronic elevation of anti-inflammatory cytokines as previously reported.

Evaluation of cytokine changes in patients with depression after 4 weeks of bupropion treatment revealed different levels of IL-4, IL-7, IFN-γ, and MCP-1, with significantly increased levels of IL-1β, IL-4, IL-5, IL-7, and IL-8 observed from baseline to posttreatment. A study by Dahl *et al*. has shown that after 12 weeks of antidepressant treatment, cytokines such as IL-1Ra, IL-6, IL-7, IL-8, IL-10, G-CSF, and TNFα were significantly reduced, with most of the treatments having a serotonergic effect.[24] Besides, previous findings regarding peripheral IL-8 levels, a pro-inflammatory role, and functions are mixed.[25] High levels of circulating IL-8 reduce the infiltration of neutrophils at the inflammation site, thereby inducing an anti-inflammatory effect.[26] Our findings are consistent with a previous study, which indicated that bupropion administration may increase inflammatory responses at both the transcriptional and translational levels by upregulating Toll-like receptor (TLR) 2, TLR4, Janus kinase 2, and signal transducer and activator of transcription 3 but significantly decrease the secretion of anti-inflammatory cytokine, such as IL-10.[27] It is important to be aware of the levels of both inflammatory and anti-inflammatory cytokines during treatment with antidepressants.[28]

In the present study, the concentration and variability of bupropion within the human brain were not tested, which could influence the increase in pro- or anti-inflammatory cytokines. An *in vitro* study showed that different selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors have contrasting effects on the production of two inflammatory markers TNF-α and free radical nitric oxide. All selective serotonin reuptake inhibitors inhibited TNF-α production, but only fluoxetine, sertraline, and paroxetine reduced free radical nitric oxide production.[28] Moreover, antidepressants possess the capacity to be both pro- and anti-inflammatory at different levels and on the length of exposure,[28] contributing in more than one way to immune modulation. It is difficult to ascertain the specific interaction between each cytokine, as certain cytokines play a unique role in the pathophysiology and recovery of depression, whereas others could represent secondary factors not directly related to depression. The significant increase in the concentration and percentage change of anti-inflammatory cytokines after treatment with bupropion may provide clinical benefits and an important role in depression.

This study has some limitations. The generalizability of the findings is limited by the small sample size, gender

limitation, wide range of illness duration, and uncontrolled covariates, including smoking status, lifestyle, or other medication combinations. Second, although there is evidence suggesting that peripheral cytokine levels are associated with cytokine levels in the brain, the increased cytokine levels in the patients treated with bupropion only reflect the cytokines in the cerebrospinal fluid. Third, although we studied several cytokines, the results do not reflect changes in the whole immune response, such as abnormalities in immune cells. Future studies should analyze other immune cells to provide a comprehensive understanding of the changes in the immune network response in depression.

CONCLUSION

Four-week bupropion treatment modulated the immune and inflammatory effects and reduced depressive symptoms in patients with MDD. Further research is needed to clarify the relationship between cytokine changes and antidepressants with specific monoamine transmission.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Drs. Yeh and Liang, upon reasonable request.

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Nil.

Conflicts of interest

Dr. Chia-Kuang Tsai, an editorial board member at *Journal of Medical Sciences*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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Supplementary Table 1: *P* value for within-group comparisons after 4-week bupropion treatment and the interaction group × time effect

	Depression	Controls	F1,39	*P*
IL-1b	0.26	−0.771	7.139	**0.011**
IL-2	−0.439	−1.567	0.168	0.684
IL-4	1.051	−0.711	5.998	**0.019**
IL-5	0.756	−1.015	5.971	**0.019**
IL-6	1.489	−2.385	1.985	0.167
IL-7	2.407	−5.002	5.802	**0.021**
IL-8	3.584	−3.137	5.641	**0.023**
IL-10	−3.535	−8.702	0.034	0.854
IL-12	−9.113	−8.674	0.024	0.879
IL-13	2.801	−0.328	0.366	0.549
IL-17	2.134	−4.032	1.688	0.202
G-CSF	3.901	−4.001	3.483	0.070
GM-CSF	−0.703	0.659	0.135	0.748
IFN-g	78.453	−34.823	4.056	0.051
MCP-1	−18.084	1.18	2.159	0.150
MIP-1b	−10.102	4.225	1.965	0.169
TNF-a	−0.766	−4.058	1.751	0.194

*Significant effects were marked with bold characters ($P<0.05$).
CI=Confidence interval; G-CSF=Granulocyte colony-stimulating factor; GM-CSF=Granulocyte-macrophage colony-stimulating factor; HDRS=Hamilton Depression Rating Scale; IFN=Interferon; IL=Interleukin; MCP=Monocyte chemotactic protein; MIP=Macrophage inflammatory protein; TNF=Tumor necrosis factor