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Evaluation of Inflammatory Markers in Patients with Depressed Episodes in Major Depressive Disorder and Bipolar Disorder before and after Treatment

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ABSTRACT

Depression is one of the current dilemmas in both developed and developing societies. Studies show that the severity of psychiatric symptoms is directly related to the degree of inflammation caused by cytokines secreted by the immune system. Hence, evaluating serum cytokine levels in patients with depression can help to understand the pathogenesis of the disease and make the best therapeutic decisions. The present study investigated the levels of inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) in patients with major depression or bipolar disorder during depressive episodes (BDDE) before and after a 6-month pharmaceutical intervention.

Patients referring to 3 clinics were recruited for the study. The diagnosis of major depression or bipolar disorder in a depressive phase was made according to the Diagnostic and Statistical Manual of Mental Disorders -5(DSM-5) criteria.

There was a significant difference in depression levels between the pre-intervention and 6-month follow-up in both groups. After 6 months, IL-1 and IL-6 levels in the bipolar disorder group had decreased while TNF-α levels had increased. There was also a significant difference between pre-intervention and follow-up levels of IL-1. Serum levels of IL-1 and IL-6 decreased significantly

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in both groups after the 6-month follow-up, and symptom improvement was observed. TNF-α levels, on the other hand, decreased in the major depression group but increased in the bipolar disorder group.

Considering that inflammation is a major outcome of depression, treatment strategies to reduce inflammation could be a practical approach to improving psychiatric symptoms.

Keywords: Bipolar disorder; Inflammatory cytokines; Interleukin-1; Interleukin-6; Major depressive disorder; Tumor necrosis factor-α

INTRODUCTION

Depression is a prevalent psychiatric disorder worldwide. According to the World Health Organization report 2020, more than 300 million people of different ages have depression worldwide; a recent study found that 12.7% of the participants had major depression.[1] A systematic review indicated a 4.1% prevalence of major depression. Depression is more common in women and the residents of countries with a moderate human development index.[2,3] A recent meta-analysis found that the prevalence of depression increased up to 7 times after the COVID-19 pandemic in 2020 due to the resulting restrictions (i.e., home quarantine and social distancing), stress caused by the death of loved ones, and reduced recreational and outdoor activities.[4] This motivates rehabilitation for depression as an effective technique to promote mental health and a normal life.

In the last decade, the assessment of biomarkers has helped significantly in diagnosing and evaluating patients with depression.[6] like inflammatory cytokines, some of these biomarkers, such as C-reactive protein and cortisol, cause changes in the brain's noradrenergic and serotonergic systems, leading to mood swings .[6] Some inflammatory cytokines secreted by immune cells disrupt the activity of brain neurotransmitters norepinephrine and serotonin, leading to mood dysregulation.[7,8]

Evidence shows that psychiatric medications control and reduce symptoms in psychiatric disorders such as schizophrenia by reducing inflammatory factors. [9] Significant changes are also reported in the level of immune biomarkers in major depression and bipolar disorder .[10]It seems that the production of inflammatory cytokines by immune cells is associated with the severity of symptoms in psychiatric disorders, especially depression caused by inflammation. These findings suggest a diagnostic role for immune biomarkers in the pathophysiology of depression and appropriate immunological interventions in its treatment.6 In this regard, interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF)-α have been investigated more thoroughly.[11] In contrast, fewer studies have compared the pattern of immune system changes in the 2 major groups of depression disorders: bipolar disorder during a depressive episodes (BDDE) and major depression.[12] Generally, evidence supports the relationship between inflammatory changes and depression.

One factor demonstrating the role of inflammatory changes in depression is increased serum levels of inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, in patients with depression. According to the findings of a meta-analysis, TNF-α and IL-6 levels increase in patients with major depression compared to healthy individuals.[13,14] Studies reported higher serum levels of IL-1, IL-6, and TNF-α in patients with major depression and bipolar disorder, compared to healthy individuals. [15-19] Elevated TNF-α levels are reported in both the manic and depressive phases of bipolar disorder.[20] According to studies by Leonard et al. and Gupta et al., serum levels of IL-1 and TNF-α were significantly higher in patients with depression compared with healthy individuals.[21,22]

Another indicator of the relationship between inflammatory changes and depression is the comorbidity of depression with inflammatory diseases, such as coronary artery disease and rheumatoid arthritis.[23-24] The relationship between the level of peripheral inflammatory markers and the severity of depression , inhibition of inflammatory markers during antidepressant therapy, and the antidepressant effects of some anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs , also support this hypothesis. Additionally, treatment with inflammatory cytokines such as IFN-γ can cause depression. [14,25,26,27]

The identification of immune biomarkers can help in screening methods, predicting the susceptibility to major depression and bipolar disorder, understanding the pathogenesis of the disease, and finding a therapeutic

solution. However, there is much controversy regarding this issue, with no data on inflammatory markers of major depression and bipolar disorder in the Iranian population. This study aimed to investigate the serum levels of inflammatory cytokines (TNF-α, IL-1, and IL-6) in patients with BDDE or major depression before and 6 months after the intervention.[11]

MATERIALS AND METHODS

The present quasi-experimental study with a before-and-after intervention design was conducted in patients with major depression or BDDE. Patients were referred to the psychiatric clinic of Imam Khomeini Teaching Hospital and 2 private centers from December 2018 to December 2020.

The inclusion criteria were as follows: 1) Age 20 to 55 years; 2) having received a diagnosis of BDDE or major depression in a clinical interview with a psychiatrist based on DSM-V diagnostic criteria; 3) no use of psychiatric drugs in the last two months; 4) ability to understand and respond to given questions; 5) and literacy.

Patients with acute and chronic inflammatory disorders, allergies, coagulation disorders, congenital and acquired immunodeficiency disorders, psychotic disorders, end-stage diseases, smokers, substance and alcohol addicts, those abusing drugs affecting the nervous system, those taking immunosuppressive drugs such as corticosteroids or gold salts, and those unwilling to cooperate were excluded from the study.

Depression or BDDE were diagnosed by a psychiatrist through the clinical interview, based on DSM-5diagnostic criteria. Out of 50 eligible patients enrolled in the study, 24 patients (8 with BDDE and 16 with major depression) completed the study course. Participants with major depressive disorder were on fluoxetine with different dosages according to their symptoms, and patients during the BDDE were receiving lithium with the appropriate therapeutic dose. The treatments were continued throughout the course of the study.

The study process, its duration, and the measures were explained to the subjects, and written consent was obtained. Demographic information about the subjects, including age, gender, and disease severity, was recorded in a form. The Hamilton Depression Rating Scale (HDRS) was completed for all the participants before the intervention and after 2 and 6 months of follow-up to assess the disease severity. Shabani et al. have estimated the validity of the HDRS at 81%.[28] The patients were visited monthly and HDRS was completed before intervention, as well as at the 2- and 6-month follow-ups and recorded together with the patient's blood sample analysis laboratory results.

Blood samples (2 mL) were taken at the onset of the study (before intervention) and at the 6-month follow-up visit to evaluate cytokine serum levels. Blood samples were transferred to the Serology Unit at Molecular Immunology Research Center, Tehran University of Medical Sciences, for serum separation. The samples were centrifuged and the separated sera were then transferred to smaller tubes and recentrifuged for 5–10 minutes at 1800 rpm to obtain clear serum samples, which were subsequently stored at −70°C. The samples were analyzed using enzyme-linked immunosorbent assay (ELISA) with human TNF-α, IL-6, and IL-1 β ELISA kits, according to the manufacturer's instructions. Serial dilutions were prepared for standard specimens. A standard curve was plotted, and the serum level of the samples was estimated.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran. The study process was explained to participants before enrollment, and the subjects signed a consent form. They were also assured of the confidentiality of their information and their right to withdraw from the study at any time.

Data were analyzed by SPSS version 25 using the Kolmogorov-Smirnov test for normalization and the t test and Mann-Whitney U Test for numerical data. A p value of <0.05 was considered statistically significant.

RESULTS

In the present study, 24 subjects completed the 6-month intervention, of whom 8 (33.33%) had BDDE and 16 (66.67%) had major depression. The mean age was 38.5 and 27 years in the major depression and bipolar disorder groups, respectively. The majority of the study participants were female (79.2%). The gender frequency distribution in the study groups is shown in Table 1.

Depression Rate

The mean score of depression, according to HDRS, in the major depression group before the intervention was 18.56, which dropped to 14.56 and 12.62 two and six months after the completion of the treatment course,

respectively. It was also reported at 23, 17.25, and 15 in the BDDE group before the intervention and at 2- and 6-month follow-ups, respectively. Table 2 shows the depression scores before and after the intervention in the two groups.

The results of the present study did not show significant differences in the mean score of depression before and 2 months after completion of the intervention in the major depression group using the *t* test (*p=0.356*); however, it was significantly different from that of the 6-month follow-up (*p*=0.04). The assessment of depression severity in the bipolar disorder group did not show no significant differences in mean depression scores before and 2 months after completion of the intervention (*p*=0.335); however, it was significantly different from that of the 6-month follow-up (*p*=0.01).

Table 1. Gender distribution of patients in the study groups

Group	Male	Female
Bipolar disorder during a depressive episode (BDDE)	32.5%	67.5%
Major depression	12.5%	87.5%
Total	20.80%	79.20%

Table 2. Mean depression score in the study groups

Group		Mean Score of Depression	*p*
Major depression	Before intervention	18.56±7.00	0.04*
	2-month follow-up	14.56±8.74	
	6-month follow-up	12.62±7.87	
Bipolar disorder during a depressive episode (BDDE)	Before intervention	23.00±3.50	0.01*
	2-month follow-up	17.25±5.36	
	6-month follow-up	15.00±6.23	

*Statistically significant (*p value<0.05*)

Pro-inflammatory Cytokines

Although not statistically significant, the serum level of IL-1, IL-6, and TNF-α reduced in the major depression group after the completion of the intervention. The serum levels of IL-6 and IL-1 also decreased in patients with BDDE, but were significant only for IL-1 (*p*=0.04). TNF-α serum levels, on the other hand, increased after intervention in the bipolar disorder group, albeit not statistically significant (Figures 1 and 2).

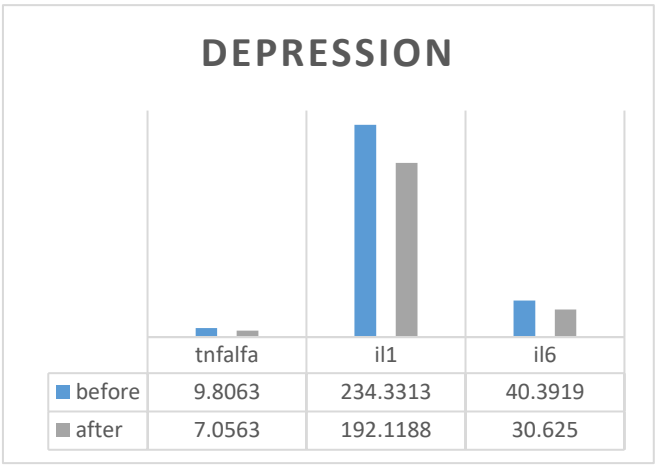

Figure 1. Mean distribution of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6, in patients with major depression before and after the intervention. The difference in the serum levels of these cytokines before and after the intervention was not statistically significant.

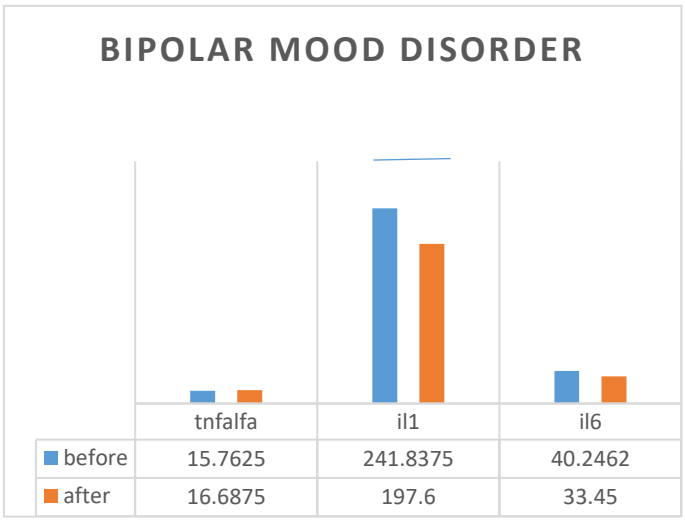

Figure 2. The mean distribution of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), in patients with bipolar disorder in the depression episode (BDDE) before and after the intervention. The IL-1 serum level decreased significantly after the intervention. However, other changes (a decrease in IL-6 and an increase in TNF-α) were not statistically significant.

DISCUSSION

In the present study, the mean scores of depresion significantly decreased at the 6-month follow-up compared to before intervention in both groups; however, no significant changes were observed at the 2-month follow-up. In addition, among the measured inflammatory cytokines, IL-1 and IL-6 serum levels decreased in the major depression and BDDE group at the 6-month follow-up. Similarly, TNF-α serum levels in the major depression group decreased 6 months after the intervention. TNF-α serum levels, on the other hand, increased in the bipolar disorder group, though the changes were significant only for IL-1 in this group.

A meta-analysis found that antidepressant therapies significantly reduce serum IL-1 levels in patients with major depression; however, similar results were not obtained for TNF-α and are inconclusive for IL-6. In

their study, the treatment of depression with SSRIs significantly reduced the serum levels of 3 cytokines.[29] Other meta-analyses, however, found a significant inverse relationship between antidepressant treatment and IL-6 and TNF-α.[30,31] It was also shown that antidepressants could reduce inflammatory factors, which are innate immune function indices; however, the effect of these agents on the acquired immune system was not entirely clear.[32]Another systematic review published in 2016 on the effects of antidepressants on the innate and acquired immune systems found that the use of these agents could lower serum level of TNF-α, IL-1, and IL-6.[33] These controversies among these particular studies could be due to different analysis methods and differences in inclusion and exclusion criteria for the meta-analysis. Nonetheless, this indicates the importance of original studies to be carried out to address this issue properly.

The current study results also revealed that in addition to significantly reducing the severity of depression, antidepressants could lower serum levels of IL-1, IL-6, and TNF-α. However, the decrease in these biomarkers was not significant in the study and needs further research on a larger sample size over a longer period of time.

A systematic review by van den Ameele analyzed studies examining the effect of mood-stabilizing medications on the serum level of inflammatory cytokines in patients with bipolar disorder.[34]They published 2 studies on untreated depression: one with a small sample size showed elevated TNF-α and IL-6 levels but normal IL-1β. [35] In another study on the serum levels of IL-1β and IL-6 after treatment with lithium drugs for 6 months, no significant difference was observed from those of normal controls . [36] In a study on patients with similar conditions, the drug was administered for an extended period of time (>5 years), and no significant difference was observed in TNF-α serum levels of healthy controls, and lithium drugs could reduce the serum level of tested cytokines to the reference range.[37] Likewise, Valvassori showed that treatment with lithium drugs decreased the serum levels of TNF-α and IL-6.[38] A study by Uyanik in patients with type 1 bipolar disorder showed that serum levels of IL-6 and TNF-α significantly reduced after treatment, and another study reported a decrease in TNF-α levels in patients receiving lithium drugs.[34,39]

Some studies on increased serum levels of IL-1, IL-6, and TNF-α—whose baselines were already higher in patients with major depression or bipolar disorder compared to controls—reported a significant decrease in IL-6 serum levels after treatment in patients with major depression and a significant decrease in IL-1 serum levels in those with bipolar disorder during the manic phase.[40]

The present study findings could not confirm the decreasing effect of lithium drugs on TNF-α serum levels in patients with BDDE and the treatment could only significantly reduce serum IL-1 levels but not IL-6 levels. The difference between these findings could be attributed to the different sample sizes imposed in the present study by COVID-19 pandemic restrictions.

Studies show that antidepressants have a reducing effect on the serum level of inflammatory cytokines. Regarding patients with bipolar disorder, the results vary depending on the disease phase. In some studies that examined changes in inflammatory cytokines during a depressive phase of bipolar disorder before and after treatment, IL-6 and IL-1 decreased after treatment; however, TNF-α levels were either increasing or decreasing.

To the best of the authors' knowledge, the present study is the first to compare the serum level of inflammatory cytokines before and after intervention in patients with major depression or BDDE in the Iranian population. The present study seems to provide reliable information on the serum level of inflammatory cytokines in patients with major depression or BDDE after antidepressants treatment.

According to the present study, the serum levels of IL-1 and IL-6 decreased significantly in major depression and BDDE group at 6-month follow-up, along with improvement in symptoms. As changes in serum level of inflammatory cytokines are directly related to depression, the administration of cytokine-reducing drugs in combination with antidepressants has a synergistic effect and is helpful in the treatment of depression; however, further multicenter studies with different treatment periods and drug combinations seem essential. Finally, it should be noted that inflammation is one of the most important conditions occurring in depression, leading to the exacerbation of symptoms, so in designing treatment strategies, the reduction of inflammation has to be considered.

The main limitation of the study was the small sample size imposed by the COVID-19 pandemic restrictions and the loss of patients to follow-up. Therefore, the results should be interpreted with more

caution due to the small sample size, and the study should be repeated on a larger sample size, for which multicenter studies can be performed.

STATEMENT OF ETHICS

This study has been approved by ethics committee of Tehran university of medical sciences. (IR.TUMS.VCR.REC.1396.4247)

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Sharifi V, Amin-Esmaeili M, Hajebi A, Motevalian A, Radgoodarzi R, Hefazi M, et al. Twelve-month prevalence and correlates of psychiatric disorders in Iran: the Iranian Mental Health Survey, 2011. Arch Iran Med. 2015;18(2):12-5.
2. Sadeghirad B, Haghdoost A-A, Amin-Esmaeili M, Ananloo ES, Ghaeli P, Rahimi-Movaghar A, et al. Epidemiology of major depressive disorder in Iran: a systematic review and meta-analysis. Int J Prev Med. 2010;1(2):81-9.
3. Sagar R, Pattanayak RD. Potential biomarkers for bipolar disorder: Where do we stand? Ind J Med Res. 2017;145(1):7-9.
4. Bueno-Notivol J, Gracia-García P, Olaya B, Lasheras I, López-Antón R, Santabárbara J. Prevalence of depression during the COVID-19 outbreak: A meta-analysis of community-based studies. Int J Clin Health Psychol. 2021;21(1):100196.
5. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. Sci Rep. 2018;8(1):1-10.
6. Teixeira AL, Colpo GD, Fries GR, Bauer IE, Selvaraj S. Biomarkers for bipolar disorder: current status and challenges ahead. Expert Rev Neurother. 2019;19(1):67-81.
7. Haapakoski R, Ebmeier KP, Alenius H, Kivimäki M. Innate and adaptive immunity in the development of depression: an update on current knowledge and technological advances. Prog. Neuro-Psychopharmacol Biol Psychiatry. 2016;66:63-72.
8. Sayana P, Colpo GD, Simoes LR, Giridharan VV, Teixeira AL, Quevedo J, et al. A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. J Psychiatr Res. 2017;92(9):160-82.
9. Höglund E, Øverli Ø, Winberg S. Tryptophan metabolic pathways and brain serotonergic activity: a comparative review. Front endocrinol. 2019;10(4):158.
10. Cox D, Chan MK, Bahn S. The potential of immune biomarkers to advance personalized medicine approaches for schizophrenia. J Nerv Ment Dis. 2015;203(5):393-9.
11. Tasic L, Larcerda AL, Pontes JG, da Costa TB, Nani JV, Martins LG, et al. Peripheral biomarkers allow differential diagnosis between schizophrenia and bipolar disorder. J Psychiatr Res. 2019;119(24):67-75.
12. Becking K, Haarman BC, Grosse L, Nolen WA, Claes S, Arolt V, et al. The circulating levels of CD4+ t helper cells are higher in bipolar disorder as compared to major depressive disorder. J Neuroimmunol. 2018;319(18):28-36.
13. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'Anna M, Mascarenhas M, Vargas AE, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord. 2009;116(3):214-7.
14. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A Meta-Analysis of Cytokines in Major Depression. Biol Psychiatry. 2010;67(5):446-57.
15. Benedetti F, Poletti S, Hoogenboezem TA, Locatelli C, de Wit H, Wijkhuijs AJ, et al. Higher baseline pro-inflammatory cytokines mark poor antidepressant response in bipolar disorder. J Clin Psychiatry. 2017;78(8):986-93.
16. Farooq RK, Asghar K, Kanwal S, Zulqernain A. Role of inflammatory cytokines in depression: Focus on interleukin-1β. Biomed Reports. 2017;6(1):15-20.
17. Hayley S. Toward an anti-inflammatory strategy for depression. Front Behav Neurosci. 2011;5:19.
18. Jazayeri S, Keshavarz SA, Tehrani-Doost M, Djalali M, Hosseini M, Amini H, et al. Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-

1beta and interleukin-6 concentrations in patients with major depressive disorder. Psychiatry Res. 2010;178(1):112-5.
19. Miller ES, Sakowicz A, Roy A, Yang A, Sullivan JT, Grobman WA, et al. Plasma and cerebrospinal fluid inflammatory cytokines in perinatal depression. Am J Obstet Gynecol. 2019;220(3):271.
20. Brietzke E, Kapczinski F. TNF-α as a molecular target in bipolar disorder. Prog Neuro-Psychopharmacol. Biol Psychiatry. 2008;32(6):1355-61.
21. Gupta R, Gupta K, Tripathi A, Bhatia M, Gupta LK. Effect of mirtazapine treatment on serum levels of brain-derived neurotrophic factor and tumor necrosis factor-α in patients of major depressive disorder with severe depression. Pharmacol. 2016;97(3-4):184-8.
22. Leonard BE. Inflammation and depression: a causal or coincidental link to the pathophysiology? Acta Neuropsychiatr. 2018;30(1):1-16.
23. Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME. Coronary artery disease and depression. Eur Heart J. 2004;25(1):3-9.
24. Margaretten M, Julian L, Katz P, Yelin E. Depression in patients with rheumatoid arthritis: description, causes and mechanisms. Int J Clin Rheumatol. 2011;6(6):617.
25. Kim Y-K, Na K-S, Shin K-H, Jung H-Y, Choi S-H, Kim J-B. Cytokine imbalance in the pathophysiology of major depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2007;31(5):1044-53.
26. Na K-S, Chang HS, Won E, Han K-M, Choi S, Tae WS, et al. Association between glucocorticoid receptor methylation and hippocampal subfields in major depressive disorder. PloS one. 2014;9(1):e85425.
27. Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. J Affect Disord. 2002;72(3):237-41.
28. Shabani A, Akbari M, Dadashi M. Reliability and validity of the Bipolar Depression Rating Scale on an Iranian sample . Arch Iran Med. 2010; 13(3):217-22.
29. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacol. 2011;36(12):2452-9.
30. Haroon E, Daguanno AW, Woolwine BJ, Goldsmith DR, Baer WM, Wommack EC, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. Psychoneuroendocrinol. 2018;95(14):43-9.
31. Wang L, Wang R, Liu L, Qiao D, Baldwin DS, Hou R. Effects of SSRIs on peripheral inflammatory markers in patients with major depressive disorder: a systematic review and meta-analysis. Brain Behav Immun. 2019;79(14):24-38.
32. Munkholm K, Braüner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res. 2013;47(9):1119-33.
33. Eyre HA, Air T, Pradhan A, Johnston J, Lavretsky H, Stuart MJ, et al. A meta-analysis of chemokines in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;68(14):1-8.
34. van den Ameele S, van Diermen L, Staels W, Coppens V, Dumont G, Sabbe B, et al. The effect of mood-stabilizing drugs on cytokine levels in bipolar disorder: a systematic review. J Affect Disord. 2016;203(25):364-73.
35. Ortiz-Domínguez A, Hernández ME, Berlanga C, Gutiérrez-Mora D, Moreno J, Heinze G, et al. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 2007;9(6):596-602.
36. Knijff EM, Nadine Breunis M, Kupka RW, De Wit HJ, Ruwhof C, Akkerhuis GW, et al. An imbalance in the production of IL-1β and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. Bipolar Disord. 2007;9(7):743-53.
37. Remlinger-Molenda A, Wojciak P, Michalak M, Karczewski J, Rybakowski JK. Selected cytokine profiles during remission in bipolar patients. Neuropsychobiol. 2012;66(3):193-8.
38. Valvassori SS, Tonin PT, Varela RB, Carvalho AF, Mariot E, Amboni RT, et al. Lithium modulates the production of peripheral and cerebral cytokines in an animal model of mania induced by dextroamphetamine. Bipolar Disord. 2015;17(5):507-17.
39. Uyanik V, Tuglu C, Gorgulu Y, Kunduracilar H, Uyanik MS. Assessment of cytokine levels and hs-CRP in bipolar I disorder before and after treatment. Psychiatr Res. 2015;228(3):386-92.
40. Goldsmith D, Rapaport M, Miller B. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry. 2016;21(12):1696-709.