

ID Design Press, Skopje, Republic of Macedonia
 Open Access Macedonian Journal of Medical Sciences. 2019 Sep 30; 7(18):3064-3069.
<https://doi.org/10.3889/oamjms.2019.779>
 eISSN: 1857-9655
Global Dermatology



The Impact of Immunological Factors on Depression Treatment – Relation Between Antidepressants and Immunomodulation Agents

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Abstract

Citation: Vojvodic J, Mihajlovic G, Vojvodic P, Radomirovic D, Vojvodic A, Vlaskovic-Jovicevic T, Peric-Hajzler Z, Matovic D, Dimitrijevic S, Sijan G, Roccia MG, Fioranelli M, Lotti T. The Impact of Immunological Factors on Depression Treatment – Relation Between Antidepressants and Immunomodulation Agents. *Open Access Maced J Med Sci.* 2019 Sep 30; 7(18):3064-3069. <https://doi.org/10.3889/oamjms.2019.779>

Keywords: Depression; Inflammation; Antidepressants; Cytokines

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Received: 13-Jul-2019; **Revised:** 17-Aug-2019; **Accepted:** 18-Aug-2019; **Online first:** 12-Sep-2019

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

It is determined that 30% of patients with depression are resistant to antidepressant medication. The increased concentration of inflammation factors, such as C-reactive protein, and pro-inflammatory cytokines, have been detected in serum in these patients. It is necessary to establish new therapeutic possibilities and protocols that are created to overcome the difficulties caused by increased concentration of inflammatory biomarkers in depressive patients. The Selective Serotonin Reuptake Inhibitors (SSRIs) are considered to be the most powerful antidepressants, increasing the level of serotonin in endogenous depression, as well as in that caused by immunological mechanisms. It is believed that agents that influence cytokines, immunological signal pathways and cytokine syntheses, like the inhibitors of cyclooxygenase enzyme and other non-steroidal anti-inflammatory drugs (NSAIDs), are very important in the potential treatment of residual symptoms of depression. Treatment with cytokine antagonists is one of the potential adjuvant therapies, along with antidepressants. Signal pathways blockers, such as the inhibitors of cyclooxygenase and other NSAIDs, are in the phase of research, in terms of their antidepressant effects. Also, it has been shown that the inhibition of indoleamine 2,3 deoxygenase (IDO) and kynurenine (KYN) signal pathways in the synthesis of neurotransmitters, by application of IDO antagonists, are leading to suppression of pro-inflammatory cytokine effects. Antidepressants may have anti-inflammatory effects, depending on dose and type, and they achieve this effect through the decrease of pro-inflammatory cytokine production and increase of anti-inflammatory cytokines. Also, antidepressants modulate the humoral and cellular immune system. This work aims to summarise certain neurobiological and neuroimmunological specificities that have been observed in patients with depression, antidepressants and immunomodulation agents. The understanding of complex and heterogenic pathophysiology of depression through the prism of the altered immune system, is of major importance, in terms of better optimisation of pharmacotherapy, and options for a personalised approach in depressive disorder treatment.

Introduction

In the last 20 years, the great expansion of biological psychiatry, that is neurosciences, has been observed. They aim to decode still insufficiently explored psychiatric diseases, like depression, which is a leading cause of morbidity worldwide, because of its high prevalence. This situation is certainly the result of the development of molecular, genetic and

neuroimaging techniques that enable the changing of current viewing of causes, course and treatment of psychiatric diseases.

The understanding of the comprehensive and heterogenic etiopathogenesis of depression, that more and more implements the role of the altered immune system is of major importance for better determination of pharmacotherapy. Because numerous studies confirm the contribution of the activated immune system and its factors in the

occurrence of depressive disorder, it is necessary to modify already existing pharmacotherapy, as well as to investigate new options, in terms of immunomodulating agents. The researches done so far have shown that innate immunity is mostly involved in the pathophysiology of depressive disorder, that is the activity of pro-inflammatory cytokines. It is believed that anti-inflammatory agents that establish the homeostasis of the immune system may have a role in the reduction of depressive symptoms. The levels of biomarkers such as C-reactive protein, tumour necrosis factor (TNF) and interleukin (IL)-1, as well as IL-6, are often increased in depressive patients, especially in those that are resistant to antidepressant treatment. They account for 30% of all patients with depression [1], [2]. This is often provoked by distress because distress activates the immune system, especially the one in earlier stages of life, and more likely if there is a genetic predisposition involved. Already mentioned pro-inflammatory cytokines activate pro-inflammatory prostaglandin E2 (PGE2), which has a leading role in inflammation mediation [1].

Pro-inflammatory cytokines created and released in the brain interact with neurotransmitters, by activating tryptophan and serotonin-degradation enzymes indoleamine-2, 3 dioxygenases (IDO) and by increasing the activity of serotonin transporters. This further leads to the decrease of serotonin available in the synaptic crack. Pro-inflammatory cytokines may be the future in the establishment of more successful antidepressant therapy, because they may be the target of anti-inflammatory therapy and modifiers of cytokine signals, in terms of defined biomarkers [3]. Tryptophan/kynurenine system (KYN) that is dominantly described in studies about immunopathogenesis of depression provides the subtlest relation between depression, distress and immunity [1], [4].

Metabolic product of KYN system are neurotoxic kynuronic acid which damages certain brain regions of depressive patients, on the one hand, and leads to the decrease of neurotransmitter level, on the other [5]. Finally, it is considered that patients with activated immune system are prone to weaker reaction to standard antidepressant therapy, and there is a hypothesis that this kind of patients would better react on therapy with antidepressants, along with the augmentation with immunosuppressive agents, that are expected to stable inflammation factors in non-responders to treatment [6]. On the other hand, it has been shown that antidepressants may inhibit the production and function of peripheral brain cytokines. They may decrease the level of pro-inflammatory cytokines, with the increase of anti-inflammatory cytokine levels which also contribute to depressive symptoms reduction [7].

Role of anti-inflammatory agents as antidepressants

New possibilities in depression treatment are the target pathways by which the immune system influences the brain, such as cytokines or growth factors, as well as the activation of relevant brain immune cells, like microglial cells. Monocytes and microglial cells may be returned on a basic level of functioning by application of immunosuppressive medications, including non-steroidal anti-inflammatory agents, like Minocycline and N-acetylcysteine. Unfortunately, these agents are not investigated in psychiatric disorders quite enough, along with their potential for further and new immunosuppressive interventions. N-acetylcysteine, Minocycline and other non-steroidal anti-inflammatory agents are aggressively tested on animal models, aiming to get an estimation of their impact on behavioural abnormalities [6]. Immunosuppressive agents that are currently in the focus of interest are cytokine antagonists, most of all TNF and IL-6, non-steroidal anti-inflammatory agents, as well as certain immunomodulation agents. Also, it is determined that the inhibition of IDO and KYN pathways leads to the suppression of cytokine effects on the glutaminergic system, thus on behaviour disturbances in depression [2], [8]. The agents affecting hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoid receptors (GRs), and post-receptor signal pathways are considered as possible therapeutic possibilities, with the potential to correct the dysregulation of this endocrine axis in depressive disorder. The medications classified as anti-glucocorticoids (GR antagonists, GR agonists, dehydroepiandrosterone – DEHA, the inhibitors of steroid synthesis) have potential abilities to stabilise the inflammation associated with the activity of glucocorticoids that may have the role in brain damage in depressive patients. The studies supporting this concept of development of the potential antidepressant therapy are still in the beginning phase [6]. The agglomeration of evidence on immunological distortions plays the crucial role in further discovering of still insufficiently defined aetiology of depressive disorder, along with distinguishing single groups of patients who share immunologic, genetic and brain alterations, and also an individual response to antidepressant treatment [9]. The side effects of anti-inflammatory medications must be beard in mind, primarily severe infections due to induced immunosuppression [10].

Cytokine inhibitors

If it is supposed that cytokines are involved in depression development, then cytokine-like

antidepressants (e.g. receptors antagonists which can regulate pro-inflammatory cytokines and anti-cytokine antibodies) may improve depressive symptoms. Cytokine antagonists that are wide-spectrum anti-inflammatory cytokines, such as IL-4 and IL-10 may be more effective than cytokine antagonists which inhibit specific cytokines in depressive treatment. TNF antagonists, like Adalimumab, Etanercept and Infliximab have been used as therapeutic agents in the treatment of autoimmune diseases, such as rheumatoid arthritis, and are currently used in clinical trials in the treatment of depressive episodes of bipolar disorder [7]. Already mentioned Adalimumab, Infliximab, as well as Golimumab, are monoclonal antibodies, unlike Etanercept, which is circulating TNF receptor fusion protein. These agents have shown their potential antidepressant effects, first on animal models, and in patients with chronic inflammatory diseases, like Chron's disease, ankylosing spondylitis, along with accompanying depressive symptoms [11]. It is determined that anti-TNF therapy, like Etanercept, which is administered in patients who have psoriasis, has a potential adjuvant effect in combination with certain antidepressants [6], [10]. It is supposed that the antidepressant effect of Etanercept is a consequence of potentiation of serotonergic and noradrenergic neurotransmission, as well as of normalisation of stress hormone secretion.

Chronic therapy with Infliximab prevents the decreasing of brain neurotrophic factor (BDNF) in the hippocampus. It has been shown that chimeric monoclonal antibody Infliximab has a potential antidepressant effect in patients suffering from depression and resistant to treatment, but only in those with increased values of inflammatory factors, like CRP and TNF, in the way of preventing the binding of TNF to its surface cell receptors [1], [10]. Anti-TNF therapy affect serotonin transporters, so it may influence the efficacy of Fluoxetine, as it is described in certain researches. It is unclear if anti-TNF therapy has the effects of noradrenergic transporters. Also, it influences the increased production of BDNF, as well as the expression of the α -amino-3-hydroxy-5-methyl-4-isoxazole acid receptor (AMPA), which is the effect of Fluoxetine itself. Changes in glutamate transmission are shown to be significant in response to antidepressant treatment [11]. The researches did so far propose the hypothesis that TNF represents the regulating factor of the apoptotic cascade that can be associated with neural and glial loss in bipolar disorder [7]. In a depressive episode of bipolar disorder, TNF levels are considered as trait markers of this disorder, and TNF modulation could be the target of antidepressant therapy [3]. In some studies, the link between anti-inflammatory cytokines and therapy resistance has been found [11]. It has been shown that in a group of therapy-resistant depressive patients those with higher pro-inflammatory cytokine levels better react to the cytokine antagonists, compared to placebo. This further contributes to the significance of better

distinction of biological markers which condition the individual response to therapy and personalised treatment. Also, it should be emphasised that the TNF antagonism concept shouldn't be generalised to all therapy-resistant patients [12].

Due to the heterogeneity of depressive aetiology and its complex nature, TNF level is increased in certain patients, and decreased in others, while it remains unchanged in some of them, even after pharmacological treatment [11]. Targeting of IL-6 pro-inflammatory cytokine with human monoclonal antibody Sirukumab may be the potential therapeutic approach in depressive patients. Sirukumab is the safe and tolerable agent, capable of modifying the immune response in a healthy population, as well as in patients with inflammatory diseases, such as rheumatoid arthritis. This monoclonal antibody may represent the prototype of an agent which proves that targeting and modifying pro-inflammatory cytokines, like IL-6, can considerably affect the pathogenesis and therapeutic outcome of mental disorders, primarily depressive disorder [13].

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs, as it is already mentioned, maybe potentially used as an adjuvant option in depression treatment, together with antidepressants. First of all, it is meant to the mechanism of cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1) blocking, as well as to the reduction of oxidative stress, preventing of pro-inflammatory cytokines increasing, and thus increasing of serotonin and other brain neurotransmitters. Findings from animal and human trials have shown certain contradictories, meaning that certain studies have found the adjuvant effect of acetylsalicylate acid (ASA) and COX-2 selective inhibitor Celecoxib, mostly in combination with SSRIs [14]. In animal (rats) model, Rofecoxib – COX-2 inhibitor increases the level of serotonin in the frontal and tempo-parietal cortex, which may have an antidepressant effect. In a randomized, double-blind trial with antidepressants Reboxetine and Celecoxib, it has been shown that Celecoxib has a positive antidepressant effect, and similar results have been obtained from the studies investigating the combination of Celecoxib and Sertraline, as well as Celecoxib and Fluoxetine [1], [15]. Namely, recent studies showed that Celecoxib, as adjuvant agent together with Sertraline, more significantly improved mood disturbances in depressive patients. Compared to the nanotherapeutic approach with antidepressant, this is considered to be the consequence of IL-6 pro-inflammatory cytokine decreasing [10]. Certain animal models showed that the combination of antidepressant Bupropion and Celecoxib might be

potentially beneficial for the strategy of depressive treatment in patients with some chronic disease. It has been demonstrated that Celecoxib decreases IL-1 pro-inflammatory cytokine level, without any effect on BDNF decreasing [16].

One study on rat model investigated the influence of 3 different antidepressants (Citalopram, Sertraline and Paroxetine) and 2 NSAIDs (Ibuprofen and Indometacin) on BDNF and nerve trophic factor (NGF) releasing, that was dose-dependent, and also depended on drug combination and probably on incubation period [17]. There are certain investigations which support the hypothesis that Aspirin that is ASA may be potential antidepressant therapy, both individually and as adjuvant. Decreasing of inflammatory mediators during stressful procedures, or in any potential physiological or biochemical mechanism, may represent the possible antidepressant effect of Aspirin [18]. Some other investigations have shown that NSAIDs in general, as well as Paracetamol, inhibit the antidepressant effect of Citalopram (both in animal and human trials), unlike ASA and COX-2 inhibitors. This discrepancy is a result of different effects of NSAIDs, COX-2 inhibitors, and salicylates both on antidepressant effect. Also, increased risk of gastrointestinal bleeding and certain cardiovascular diseases should be considered during the chronic use of these medications, especially because these issues haven't been considered in earlier studies investigating the potential adjuvant effect of these drugs in depression treatment [19]. Current investigations neither support nor discourage the use of NSAIDs and Paracetamol together with antidepressant therapy, because conclusion about their favourable or unfavourable effect cannot be brought.

Further detailed investigations are necessary to make a distinction which NSAIDs is the safest, and the most potent at the same time, in terms of adjuvant therapy of depression [15].

The other anti-inflammatory drugs and potential antidepressant agents

It has been shown that the expression of Toll-like receptors (TLRs) is associated with therapeutic outcome in depressive patients that indicates the relationship between inflammation, depression and therapy. Future studies on animal models will show the possible antidepressant effect of TLR antagonists [20], [21]. Antiglucocorticoid agents, including Ketoconazole and Metyrapone, are tested to antidepressant effects, but significant achievements have not been observed due to side effects and insufficiently known clinical potential of Metyrapone. Dexamethasone and Hydrocortisone may also be

shortly useful for certain depressive symptoms. Glutamate antagonists targeting with Ketamine that is N-methyl-d-aspartate receptor (NMDA) may be possibly efficient for depression therapy. Omega-3 polyunsaturated fatty acids affect the metabolic and inflammatory activity and show certain benefits in depressive symptoms reduction. It has been demonstrated that the antidepressant effect may be mediated by statins through certain neurobiological pathways [22]. Statins are agents primarily used to decrease lipid level in peripheral blood, but also show anti-inflammatory effects. In the context of the inflammatory hypothesis of depression, certain studies have found that depressive patients who had been using statins, along with SSRIs, had had more stable remission with the rarer occurrence of relapses, compared to those who had been on monotherapy with antidepressant [1]. It is interesting to say that a high level of homocysteine in serum is also associated with the risk of cardiovascular diseases and depression. B vitamin consumption (B6, B9 and B12) decreases homocysteine level by 15%, and it is also meant that antithrombotic therapy, namely Aspirin, decreases homocysteine level. That's why in older people who use Aspirin regularly in their therapy and who have higher homocysteine level, the occurrence of depression is uncommon. However, further randomised trials are necessary to confirm this Aspirin feature in people with an increased level of homocysteine [23].

Animal model of stress-induced depression that was presented with behavioural and biochemical alteration of the already mentioned KYN pathway has shown the antidepressant effect of IDO inhibitor (1-methyl-D-tryptophane) that is very similar to antidepressant Fluoxetine. It has been observed that 1-methyl-D-tryptophane and Fluoxetine decrease the level of pro-inflammatory cytokines in this animal model, so the antidepressant effect is achieved through an anti-inflammatory effect [24].

Curcumin is diarylheptanoid and polyphenol component of *Curcuma longa* which has therapeutic and nutritive characteristics. Namely, it is shown that curcumin stimulates BDNF and inhibits COX-2 on animal (rat) models exposed to chronic distress, so in that terms has neuroprotective, possible antidepressant effects, as well as the effect on neuroplasticity [25].

Immunomodulating effect of antidepressants

Biochemical effect of antidepressants has been used because of their clinical benefits in certain medical disciplines, especially gastroenterology, neurology, and for some non-specific disease

symptoms. Anti-inflammatory effect of antidepressants may be the reason for the wide indications of their use [22]. There is certain evidence that antidepressants may have immunomodulation performances in animal models of depression.

For example, SSRI Escitalopram and Paroxetine are the agents which decrease pro-inflammatory markers (TNF, IL-1, IL-6 and PGE-2), besides the reduction of depressive symptoms. On the other hand, in certain animal models, it has been shown that Citalopram increases the level of central pro-inflammatory cytokines, like TNF and INF- γ . These may be explained by the fact that immune cells have neurotransmitter receptors, so antidepressants affect these receptors and regulate the immune activity. T lymphocytes have 5-hydroxytryptamine (5-HT) receptors (5-HT_{1A} and 5-HT_{2A / 2C}) on their surface. Macrophages express 5-HT system of reuptake that is similar to the one of serotonin's reuptake of thrombocytes. Also, antidepressants regulate cytokine-induced GR of resistance, by which they normalise HPA axis function in depression. They inhibit nitrogen-oxide and PGE₂ production which is increased by cytokine effects and inhibit IDO activity as well. They affect macrophages and lymphocytes directly, inducing them to produce anti-inflammatory cytokines [7], [26]. Also, it was shown that SSRIs (Citalopram) performed down-regulation of CD4 receptor expression, as well as chemokines receptors (CCR5, CXR4), in patients infected with human immunodeficiency virus (HIV), and that is the manner of inhibition of the virus' entrance in cells and its replication. So, it could be told that SSRIs may have an adjuvant medication role in immune restitution of patients infected with HIV and suffering or not of depression [27].

There are some indications that SSRIs stimulate B lymphocytes proliferation in depressive patients, so they affect innate immunity. The studies investigating the effect of serotonin and noradrenaline reuptake inhibitors (SNRIs) on the immune system, both innate and acquired, are scarce. It seems they have anti-inflammatory effects, and that may be dose-dependent. The effects on the immune system depend on if patients are early responders, or don't respond to the therapy with SNRIs. It was found that they affected certain lymphocytic gene expression, so they influence migration, remodelling of cytoskeleton, and activation of lymphocytes. There is a small number of studies which estimate Venlafaxine and Duloxetine influence on inflammation markers. The fact is that they influence the levels of Th1 and Th2 type of cytokines [28]. The theory is that SSRIs target Th2 shift during the inflammation, while SNRIs affect Th1 shift [22]. Certain researches show more potent effects of SSRIs compared to SNRIs. When it is about tricyclic antidepressants, there are also a few studies investigating their influence on innate and acquired immunity, but it is generally accepted that they have anti-inflammatory effects, especially by decreasing the

efficacy of acquired immunity, that is T lymphocytes. The small number of studies is about the influence of antidepressants on chemokines and represents the field that is necessary to investigate further. Until now, there has been only one study investigating the effects of antidepressants on cytokines in cerebrospinal fluid (CSF). It is necessary to include more recent antidepressants in further studies, like Agomelatine, serotonin and melatonin active agent, because it is believed that it has anti-inflammatory effects [28]. Few studies are investigating the immunomodulation effect of SSRIs, SNRIs and monoamine oxidase inhibitors (MAOIs) [29]. It is suggested that decreased level of cytokines after antidepressant treatment may be connected to the increase of T regulatory cells number. Also, the immunomodulation effect of electroconvulsive therapy (ECT) has been shown in certain studies [10].

Conclusion

The treatment of psychiatric disorders is high economic burden nowadays, even though the investments in the researches on alterations in molecular brain nets represent the platform for new therapeutic strategies, which is one of the greatest pharmacological and research challenges in XXI century.

So, what can be concluded until now with great caution, is that anti-inflammatory therapy can potentially be adjuvant treatment together with antidepressants, on the one hand, while antidepressants on the other, especially those of new generation, show inhibitory effects on immune processes. Finally, the interaction between neurotransmitters and innate and acquired immunity should be thoroughly investigated. At this moment, it is very hard to bring out definite conclusions, because there are still not enough evidence and researches which could confirm the clear and undoubted role of immune mechanisms in the pathogenesis of depression, and consequently the influence of anti-inflammatory drugs on its therapy. Further studies should define methods which would single out the components of the immune system in different neuroanatomic regions. More specifically, their role is to complete the palette of biomarkers which would enable a personalized approach to every single patient and deal with dilemmas referring to resistance to medications. Neurobiological and neuroimmunology studies done so far only partly explained complex pathophysiology of depressive disorder, so numerous proposed therapeutic interventions are still in conceptual and preclinical stages.

It is very important to emphasise that those immunomodulation drugs for which there are significant indications of clinical benefits should pass

the phase of more thorough testing on tolerability, efficacy, and safety, so after that, their implementation into therapeutic protocols for depression treatment can be considered.

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