REVIEW ARTICLE

# Is depression an inflammatory condition? A review of available evidence

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## Abstract

The current review examines the relationship between depression and the inflammatory immune response. Mood disorders are a significant cause of morbidity and the etiology of depression is still not clearly understood. Many studies have shown links between inflammatory cytokines and mood disorders, including elevated level of cytokines like tumour necrosis factor-alpha (TNF $\alpha$), Interleukins (IL-1,IL-6) and others. Raised levels of cytokines have been shown to increase depressive behaviour in animal models, while many anti-depressants reverse this behaviour alongside reducing the Central Nervous System (CNS) inflammatory response and reduction in the amounts of inflammatory cytokines. Cytokines reduce neurogenesis, Brain Derived Neurotrophic Factor (BDNF) and neuronal plasticity in the CNS, while many anti-depressants have been shown to reverse these processes. The considerations of anti-depressants as anti-inflammatory agents, and implication of other anti-inflammatory therapeutics for the treatment of depression are pointed out.

**Keywords:** Depression, Inflammation, Cytokines.

## Introduction

Mood disorders, especially depressive disorders are prevalent, hard to treat and cause considerable morbidity. There is a bidirectional relationship between mood disorders, especially depression and markers of the inflammatory immune response, such as Interleukins and Interferons. In the last 25 years several new classes of anti-depressant medications have become available for the treatment of these debilitating conditions. While the in vitro effects of these medications have been clearly elucidated, their exact mechanisms of in-vivo action are still disputed. Animal models of depression including measurement of cytokine levels, have provided some clues about both the pathophysiology of depression as well as the mechanism of action of commonly used anti-depressant medication. In this paper we review the available evidence about the role of inflammatory cytokines in the etiology of depression and the relationship between anti-depressant medication and cytokine levels in the body both before and after treatment.

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## The Burden of Depression

Depression is a complex illness that is associated with substantial disability and reduced quality of life for the person with depression, as well as a significant social burden. Major depressive disorder (MDD) is the occurrence of one or more episodes of major depression. A Major Depressive Episode (MDE) is defined as a period of at least 2 weeks that is characterised either by depressed mood and/or markedly diminished interest or pleasure in all, or almost all, activities in addition to at least four other symptoms.[1] Dysthymic disorder is characterised by a chronically depressed mood and at least two other depressive symptoms that occur most of the day, more days than not, for at least 2 years.

Mood disorders, including MD, affect as many as one in five individuals and are the most prevalent psychiatric conditions.[2] The World Health Organisation (WHO) projects that MD will be the second leading cause of disability worldwide by 2020.[3] The lifetime risk of MDD in the USA is 7% to 12% for men and 20% to 25% for women.[4]

There are no, large, well-designed population-based studies of the incidence and prevalence of depression in Pakistan. However, the available studies indicate a prevalence of MDD in Pakistan to be between 10% and 50%.[5-7] Most individuals with MDD have a chronic or recurrent course, often with considerable symptomatology and disability even between episodes.[8-10] Approximately one-third of MDD are refractory to any kind of anti-depressant treatment, including selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs), monoamine oxidase inhibitors (MAOIs), and electroconvulsive therapy (ECT).[11]

Depression has a significantly negative impact on occupational functioning. In one study, comparing workers with depression and workers with rheumatoid

arthritis, depressed workers had significantly greater performance deficits than the controls. This included performing mental tasks, time management, output tasks, and physical tasks.[12] Depressed employees are also almost five times as likely to lose their jobs as those with arthritis.[13]

Depression negatively impacts physical health as well; it reduces compliance with medical treatment[14] and increases the likelihood of risk factors such as obesity,[15] smoking[16] and a sedentary lifestyle.[17]

MDD can also be associated with multiple medical conditions, including cardiovascular disease[18] endocrine and neurological diseases, and a general increase in chronic disease incidence.[19] Mortality rates in MDD are also high; approximately four per cent of people with a mood disorder commit suicide and about two-thirds of suicides are preceded by depression.[20]

Untreated depression in adolescents results in significant decline in school performance, interpersonal relationships, risk of early pregnancy and impaired social and family functioning.[21] It also impairs occupational adjustment and increases the risk of suicidal behaviour and completed suicide.[22]

## Cytokines and Depression

It has become clear that the inflammatory immune system is altered during the course of clinical depression. Most of the evidence that links inflammation and MDD comes from three observations:[23]

1. MDD (even in the absence of medical illness) is associated with raised inflammatory markers.

2. Inflammatory medical illnesses, both CNS and peripheral, are associated with greater rates of major depression.

3. Patients treated with cytokines for various illnesses are at increased risk of developing major depressive illness.

Acute stress enhances immune function while chronic stress suppresses it through the Hypothalamic-Pituitary-Adrenal (HPA) axis.[24] Elevated glucocorticoids released in response to acute stress activate the 'delayed-type hypersensitivity' (DTH) response; so called because it occurs 24-72 hours after an environmental threat.[25] Chronic stress leads to habituation of the HPA axis response and thus impairs the DTH response.[25]

Various psychological stressors can induce neurotransmitter changes which include disturbed functioning of the adaptive immune system, including T and B lymphocytes, as well as innate immune cells, particularly natural killer (NK) cells and macrophages.[26] Although the blood-brain barrier (BBB), as well as other inhibitory mechanisms, within the brain, normally tightly regulate the flow and level of immune factors within the brain, increasing evidence-indicates that several neurological disorders, including multiple sclerosis, Alzheimer's and Parkinson's disease, have a prominent neuro-inflammatory component.[27-29]

In addition to direct entry into the brain parenchyma, immune factors can influence CNS functioning through activation of receptors located on peripheral organs or the BBB.[30]

Cytokines are soluble low-molecular-weight glycoprotein messengers secreted by lymphoid cells which act as signallers to other lymphoid cells. They can be classified into various groups, including Interferons (released by infected cells and induce anti-viral resistance), Interleukins (abbreviated as IL; produced mostly by T-cells and involved in directing other cells to divide and differentiate), Colony stimulating factors (direct division and differentiation of bone marrow stem cells) and other cytokines such as tumor necrosis factors (TNF) which mediate inflammation and cytotoxic reactions.[31] Cytokines are often divided into pro-inflammatory (including IL-1, IL-6 and TNF) or anti-inflammatory (IL-4, IL-10, IL-13).[32]

Cytokines influence brain functioning in a variety of ways. They can bind to receptors located on the liver or spleen or the nodose ganglion and trigger neural firing from these sites, which can then signal the CNS.[33] They can also interact directly with BBB receptors to induce cyclooxygenase-2 (COX2) inflammatory signalling within the brain parenchyma.[34,35] There is also evidence that they are produced in CNS glial cells.[36]

Cytokines are important for a subset, but not all depressive symptoms. It is helpful to view cytokines as being a very important trigger that acts together with psychosocial challenges to provoke the onset of MDD. They have potent sickness-inducing effects (so called 'sickness behaviour' including social withdrawal, reduced appetite and low energy), which are often taken to reflect some form of depression.[37,38] On the other hand, the melancholia typical of MDD is harder to model in animals and might be somewhat independent from cytokine effects.

## Classes of Anti-Depressant Drugs and Their Actions

Most anti-depressants enhance noradrenergic and/or serotonergic neurotransmission

following acute administration.[39] For the most widely used anti-depressants, including TCAs, SSRIs), norepinephrine reuptake inhibitors (NRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), this results from reuptake inhibition of norepinephrine or serotonin in the neuronal synapse.[40-43] Some drugs enhance monoaminergic neurotransmission by other mechanisms such as inhibition of monoamine oxidase,[44,45] or antagonism of presynaptic alpha-2 adrenergic receptors.[46-48] The exact relationship between synaptic monoamine neurotransmission and the efficacy of antidepressant medications remains unclear. Although monoamine levels begin to rise within hours of the first administration of the drug, its therapeutic effects develop gradually over time with repeated treatment.[49,50] This discrepancy has focused research on non-monoamine mechanisms that may lead to more effective anti-depressants.[39]

## Animal Models of Depression

In addition to being a major public health problem, the treatments available for depression leave much to be desired. Even if MDD is accurately diagnosed and adequately treated with excellent compliance, remission rates with standard anti-depressants vary from 30-40%.[39,40] In contrast other chronic disorders such as diabetes mellitus can be adequately treated with successful prevention of complications in a large majority of patients.[41]

This has been presumed to be because of several factors. First, the diagnosis of depressive episodes is based primarily on 'check lists' of certain vaguely defined clinical symptoms (e.g., depressed mood, anhedonia, sleep changes, appetite changes, guilt, etc.) for a 2-week period. There are no objective diagnostic tools available such as neuroimaging, genetic variations, biomarkers, or biopsies. Depression is heterogeneous (atypical vs. melancholic vs. psychotic, etc.),[42] but little is known about the pathophysiological or etiological differences between these subtypes. Most current theories of depression are based largely on animal models of the disease.

Some of the core symptoms of depression in humans such as guilt, suicidal ideation and sad mood obviously cannot be assessed in animals. However, other aspects of the depressive syndrome have been replicated and in several instances ameliorated with anti-depressant treatment in laboratory animals. These include measures of helplessness, anhedonia, behavioural despair and other neuro-vegetative changes such as alterations in sleep and appetite patterns.

Animal models of depression can be categorised into those that provoke acute stress such as the Forced Swim Test (FST),[46] the Tail Suspension Test (TST)[47] or the Learned Helplessness (LH) Model, following an uncontrollable stress such as exposure to inescapable electric shocks. So called 'secondary depression' is mediated through the HPA Axis and can be secondary to external stress or iatrogenic, the effects of both of which can be studied in mice.[49,50]

Cytokines have been shown to induce depression-like behaviour in rodents and primates.[51,52] However, simply inducing 'sickness behaviour' by strong immune stimuli such as lipopolysaccharide (LPS)[53] overlooks other core symptoms of depression in humans that cannot be modelled in animals such as guilt, suicidal thoughts or melancholia.

Chronic mild stress (CMS), better described as Chronic Unpredictable Stress (CUS), involves the application of intermittent physical stresses (water deprivation, cage tilt, continuous light, white noise, damp bedding etc.) applied randomly over a relatively prolonged time period (between 1 and 7 weeks). This model has been recently used to phenotype mouse mutants, study gender differences in stress responses, and validate novel anti-depressants.[54-56]

Despite advances in our understanding of some of the mechanisms of depression, new anti-depressants slightly vary from their predecessors in side-effect profiles only, with little or no improvements in efficacy. Clinicians are often forced to initiate multiple anti-depressant medications simultaneously, or rely on adjunct medications like thyroid hormone, anti-psychotic agents or psychostimulants to boost the anti-depressant response. The animal models of depression discussed so far can expand our understanding of mechanisms in depression.

## Anti-Depressants and Cytokines Levels in Animal Models

Extensive work has been done on the effects of anti-depressant drugs on cytokine production in animal and in-vitro studies. The common approach in such studies in animals was to induce sickness behaviour by administration of bacterial LPS or by using animal models that replicate the features of depression seen in humans, as mentioned earlier, e.g., FST, TST and CMS. Another approach is use of olfactory bulbectomised (OB) rats which demonstrate increased production of pro-inflammatory cytokines.[57]

In a recent study, administration of TNF-$\alpha$ in mice resulted

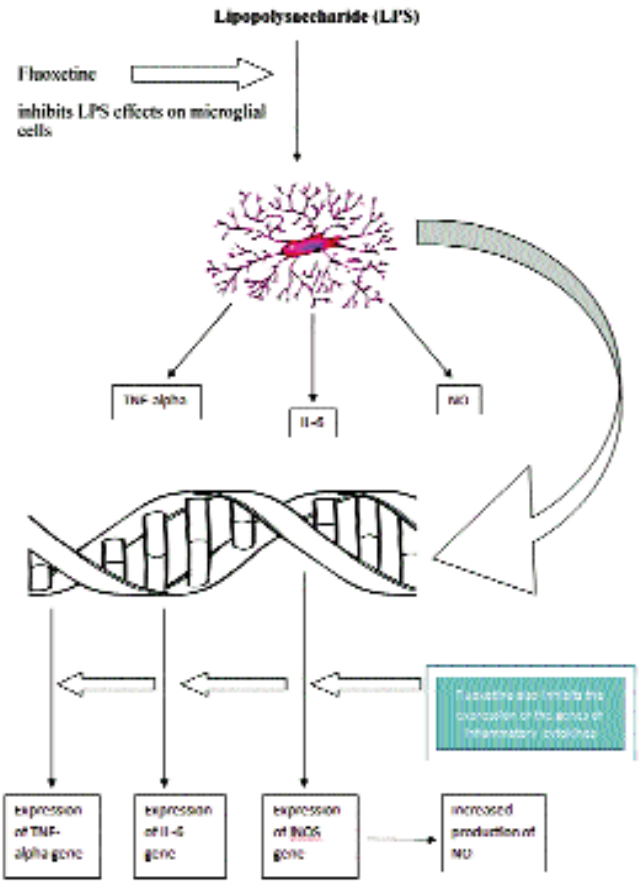
in depressive behaviour in FST and TST models. These depressive symptoms were attenuated by administration of Fluoxetine, Imipramine, and Desipramine.[58] In another study, coronary arteries of rats were blocked to produce myocardial infarction (MI). This resulted in depression-like symptoms similar to post-MI depression in humans. Administration of Escitalopram decreased despair, anhedonia and levels of TNF-α, prostaglandin E2 (PGE2,) and IL-1.[59]

Kubera et al showed that chronic administration of imipramine in CMS model reversed anhedonia and elevated production of pro-inflammatory cytokines like IL-1 and IL-2. Chronic administration of SSRIs and TCA in OB rats reversed the rise in acute phase reactants.[57] Many studies have shown that sickness behaviour in animals produced by administration of bacterial LPS can be reversed by chronic administration of different anti-depressant drugs.[60,61]

Human blood monocytes are widely used in in-vitro studies to evaluate the effects of anti-depressants on cytokine production. Kubera M et al have shown that pro-inflammatory cytokine production by human monocytes induced by bacterial LPS is inhibited by anti-depressants.[62] In another study, Fluoxetine and Citalopram were added to culture of synovial membrane cells from patients of rheumatoid arthritis. They reduced production of TNF-α, IL-6, interferone INF-γ inducible protein 10.[63]

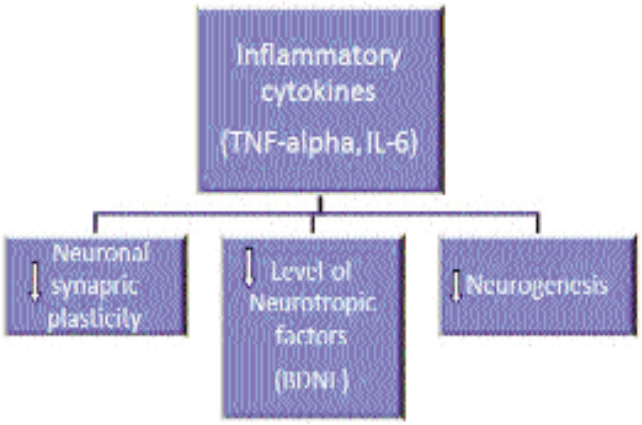
Microglial activation in brain plays an important role in pathophysiology of depression because microglia produce pro-inflammatory cytokines when stimulated. In a recent study, fluoxetine was added to LPS-stimulated microglial cells. Fluoxetine inhibited production of TNF-α, IL-6, and nitric oxide (NO) and decreased messenger Ribonucleic acid (mRNA) levels of these cytokines (Figure-1) and inducible Nitric Oxide Synthase (iNOS).[64] This demonstrates that interventions aiming at microglial activation may be a therapeutic possibility in depression. In another study, microglia were activated by administering IFN-γ. Subsequent administration of Paroxetine and Sertraline reduced production of NO and TNF-α by inhibiting IFN-γ induced raised intracellular calcium[65] (Figure-1).

Studies of the CNS of animals have also shown that increased levels of inflammatory cytokines have implications in development of depression due to disturbed neuronal synaptic plasticity and disturbances in the levels of different neurotrophic factors especially BDNF in the hippocampus.[62,64] Moreover, these increased levels of cytokines have




**TNF: Tumour necrosis factor. iNOS: Inducible Nitric Oxide Synthase. NO: Nitric Oxide. IL: Interleukins.**

**Figure-1:** Interaction between the microglia and the inflammatory cytokines. (Source: Original figure for this review).




**TNF: Tumour Necrosis Factor. BDNF: Brain Derived Neurotrophic Factor. IL: Interleukins.**

**Figure-2:** Source: Original Image.

been shown to reduce neurogenesis in the hippocampus,[62,63] while studies by Wang Y et al have shown that the administration of Fluoxetine (an SSRI) increases neurogenesis in the hippocampus by antagonising the effects of cytokines.[65] This fact is also supported by studies of the ablation of hippocampal neurogenesis, which attenuated the behavioural effects of the anti-depressants.[62] SSRIs have also been shown to potentiate the effects of neurotrophic factor BDNF in reducing the release of NO (an inflammatory cytokine, and an agent of oxidative stress) from activated rodent microglia.[66] Thus anti-depressants may play a role in reducing the release of inflammatory cytokines by glia cells, independent of their role in neurogenesis (Figure-2).

## Human Studies

Studies in humans are less conclusive than those in animals or those in-vitro. Hannestad J recently conducted a meta-analysis of 22 studies done in humans in which cytokine levels were measured before and after treatment with anti-depressants for major depression. The study concluded that TNF-$\alpha$ is not affected by anti-depressants, but anti-depressants reduce IL-1$\beta$ and possibly IL-6 levels as expected. All classes of anti-depressants reduce symptoms of depression.[67] Anti-depressants do not reduce cytokine levels in healthy subjects. In a study by the same author on healthy subjects, it was found that pre-treatment with Citalopram did not reduce elevated levels of IL-6 and TNF-$\alpha$ induced by low dose endotoxin administration, but depression severity was reduced by 50%.[68] In another study, Fluoxetine reduced IL-1$\beta$ levels in respondents only.[69] Studies have shown that addition of anti-inflammatory drugs to anti-depressants in humans results in greater degree of reduction in cytokine levels and depression symptoms. In a recent randomised controlled trial (RCT), the Celecoxib plus Sertraline group had greater reduction in levels of IL-6 and symptoms of depression than the Sertraline only group.[70] In another RCT, Celecoxib plus Fluoxetine markedly reduced depression severity compared to Fluoxetine alone.[71] The use of anti-inflammatory agents in the adjunctive treatment of depression is in need of further research and exploration before any suggestion can be made regarding their clinical use, considering that current anti-inflammatory drugs often have serious side effects of their own.

## Mechanisms of Immunomodulatry Effects of Anti-Depressants

Anti-depressants may be involved in modulating pro-inflammatory states at both micro and macro-levels. These may include alterations in hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoid receptor (GR) signalling, synaptic plasticity, neuronal regeneration, increased production of neurotrophic factors, alterations in melatonin production, changes in microglial proton channels and astrocytes favouring an anti-inflammatory state.

As described previously, decreased sensitivity of GR and disturbances in HPA axis are important in the pathophysiology of depression. Elevated cytokines in depression reduce the negative feedback control in HPA axis[72] and reduce GR expression.[73] A recent review concluded that anti-depressants up-regulate and increase GR expression, thereby restoring the negative feedback control system in HPA axis. Moreover, they also normalise serum glucocorticoid levels.[74]

As described previously, microglia produce pro-inflammatory cytokines and anti-depressants reduce microglial activation and thus production of pro-inflammatory cytokines. Anti-depressants may do this by blocking proton channels in microglia that are important in production of cytokines. In a recent study, it was found that imipramine inhibited the release of TNF-$\alpha$ from LPS-stimulated murine microglia cells at concentrations comparable to those that blocked microglial proton channels.[75]

Depressed patients have decreased melatonin levels and anti-depressant drugs increase melatonin production.[74] Melatonin is important in maintaining normal circadian rhythms and sleep-wake cycles in humans. Another mechanism by which anti-depressants may modulate effects of pro-inflammatory cytokines is their inhibitory effect on iNOS, thus resulting in decreased production of NO and PGE2.[57]

Structural changes in neuronal synapses and increased hippocampal neurogenesis after chronic administration of anti-depressant drugs has been consistently observed in animal models of depression.[76,77] Mice treated with Methyl-phenyl-tetrahydropyridine (MPTP) are used as an animal model of Parkinson's disease because MPTP administration results in neuronal damage in the nigrostriatal pathway. In a recent study, fluoxetine prevented this neuronal damage by decreasing the production of pro-inflammatory cytokines and reducing activity of nicotinamide adenine dinucleotide phosphate NADPH Oxidase, thus decreasing the generation of free radicals and reactive oxygen species.[78] Anti-depressants also promote production of neurotrophic growth factors and modulate signalling cascade in microglia.[79] It is still unknown whether changes in synaptic plasticity and neurogenesis persist

after discontinuation of anti-depressants.

## Conclusion

Variations in the levels of pro- and anti-inflammatory cytokines are central to the pathophysiology of depression. Treatment with anti-depressant medication helps normalise these variations and may play a key role in recovery from depressive illness. The exact mechanism of the immunomodulatory effects of anti-depressants is unknown, but it may involve normalisation of glucocortocoid negative feedback control, increased neurogenesis and production of neurotrophic factors and decreased microglia activation in the CNS. Cytokines are important biological markers in elucidating the mechanism and pathophysiology of depression as well as helping with diagnosis, treatment selection and long-term screening. In the light of data suggesting that immuneprocesses may interact with the pathophysiologic pathways known to contribute to depression, novel approaches to the treatment of depression may target relevant aspects of the immune response. Further research is needed, particularly on the clinical effects of cytokine antagonists and cytokine synthesis inhibitors on the pathophysiological and psychological features of MDD. The cytokine hypothesis also presents a novel opportunity for the development of a new generation of effective anti-depressants.

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