ADJUVANT THERAPY IN DEPRESSION: A REVIEW

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ABSTRACT
Major depression is a disabling disorder. With ever increasing disease burden and projected rise in disability, it is the focus of a lot of research. Although the current first line antidepressant therapy is much better in terms of safety profile than its predecessors, in terms of remission it has only a slight advantage. Main emphasis of research on depression, thus, rests on finding of treatment regimens capable of bringing sustained remission to the fateful patients with a desirable safety profile. In this pursuit, many aspects of depressive illness have been unearthed which are suggestive a lot of innovation in the treatment strategy. These include interpretation synthesis inhibitors, microglial activation inhibitors, mechanistic target of rapamycin (mTOR) pathway inhibitors, Inhibitors of tryptophan-kyneurinine pathway, corticotropin releasing factor 1 (CRF1) receptor inhibitors, P2X7 receptor inhibitors and anti-inflammatory agents. Many of these agents are under the process of experimentation for approval to be used in humans. Anti-inflammatory agents, however, are many in number and already approved for human use. Therefore, their use can be readily investigated and justifiably recommended as adjuvant in antidepressant pharmacotherapy. Here, we review clinical and pre-clinical evidence regarding some members of anti-inflammatory agents for their potential use as an additional drug in treatment of depression refractory to the first line antidepressant therapy.

NEUROBIOLOGY OF DEPRESSION
Depression is a costly public health problem that has been given tremendous emphasis in last couple of decades. Epidemiological surveys showing projected increase in the morbidity in near future has forced many organizations to dedicate substantial funds for research in this field. Advent of selective serotonin re-uptake inhibitors (SSRIs) has been very helpful mainly because of their better safety profile and consequent increase in patient compliance. Yet the achievements in terms of rate and sustainability of remission have been far from being satisfactory. If the unpublished studies submitted to Federal Drug Authority (FDA) are accounted for, the antidepressant effect of SSRIs is marginally better than placebo. This, in part, has been due to the deficiency on the understanding of pathophysiological processes involved in depressive illness. On a fundamental note, thus, the underlying difficulties in understanding of pathophysiological processes have been unearthed once after the other. What has resulted is a very complex and heterogeneous picture of the disease, its co-prevalence with vascular, Inflammatory and immune-related disorders, aging, genetic predispositions and stressful events especially during childhood. A host of theories can be found explaining the nature of the disorder, coining different terms like vascular depression. In addition to various degrees of stress, genetic predispositions, hypothalamo-pituitary-adrenal axis (HPA axis) dysregulation, vascular dysfunction, immune activation etc, have been postulated to give rise to molecular mechanism like decreased neurogenesis, proliferation and maturation, decreased size of hippocampus, alterations in neuroplasticity, decreased arterial and blood pulsatility which individually or collectively lead to eventual alterations in mood.

As stated earlier, many mechanisms have been proposed to play their role in the induction of depressive symptoms. One of the hypotheses, which earned a lot of respect, is the inflammatory hypothesis of depression initially presented by Maes et al. in successive reviews in 1993 and 1995 and later on. The data presented in two successive reviews claimed to connect the dots between activation of immune system and induction of depressive symptoms. This fact has been highlighted especially with the arrival of pro-inflammatory drugs like interferon alpha gamma, which is used to boost the inflammatory response, and is typically associated with induction of depressive symptoms. The evidence that has led to the belief that there is a connection between pro-inflammatory markers and depression can be summarized as follows.

1. An increase in the serum levels of circulating pro-inflammatory cytokines e.g. IL-1β, IL-6, and IFNγ have been observed which corresponds to the severity of depressive features and result in the acute phase response seen during depression.
2. A depressive-like state has been observed in animals as well as humans subjected to pro-inflammatory cytokines therapy such as interferon therapy in chronic viral hepatitis. Stress induced changes in serotonergic and HPA axis activity are also explained by pro-inflammatory cytokines hypothesis. UCMS induces depressive-like behavior by the activation of microglia as well as activation of kynurenic pathway of serotonin metabolism that may be called as neuroinflammation.

3. Newborn neurons are a fragile population sensitive to inflammatory changes in the environment as persistently activated inflammatory parameters decrease the number of new neurons and in turn may possibly result into mood changes and neurocognitive decline.

4. Incidence of degenerative diseases of brain is higher among the subjects previously diagnosed with depression which possibly mean that a baseline change in inflammatory balance takes place during depression which, if continued unabated, results in persistent inflammation and degeneration.

These implications have been challenged at many levels, especially for their therapeutic efficacy. Different members of anti-inflammatory drugs targeting different steps and mechanisms related to immunity and inflammation are hypothesized to contribute to the reversal of depressive symptoms. An overview of these individual drugs is presented in this review so that the idea of adjuvant anti-inflammatory treatment in depression can be understood better.

**Aging And Inflammatory Factors Accumulation**

Age-related depression is increasingly being recognized as a separate entity with various different characters. They may include a variable clinical picture, comorbidity with vascular and inflammatory disorders, precipitating factors such as chronic inflammatory conditions, its effect on prognosis of other diseases and an altered response to first line antidepressant treatment. So it is being named as geriatric depression. Vascular and inflammatory derangements seem to play a pivotal role in deterioration of mental state along with age. It is important to look for evidence of these derangements in clinical profiles. It will help establish the case for formulation of future therapeutic guidelines.

The debate can be addressed under two heads, the effects of antidepressant medicine in addition to/other than their direct antidepressant effect and antidepressant effects of “other” medicine in addition to their usual action.

**Anti-inflammatory effects of antidepressant (AD) drugs**

Evidence states that anti-depressant drugs help calm down the inflammatory rage. The mechanisms, however, are hypothesized and are many. One is that they inhibit the activation of microglia. The other proposed mechanisms include lowering of pro-inflammatory cytokine concentration, decreasing the cortisol synthesis and re-instatement of deranged neuroendocrine axis among others.

Fluoxetine has been found to be effective in lowering of pro-inflammatory cytokine levels in blood, Venlafaxine has been shown to abolish the neuroendocrine mode of stress cascade. Such findings have been endorsed by many other studies as well.

**Antidepressant (AD) effects of anti-inflammatory drugs**

**Minocycline**

Minocycline has also been associated with inhibition of microglial activation and has being tested for its potential protective role against neurocognitive decline associated with many psychiatric conditions. It has been used for its effects on neural plasticity and neurocognitive decline in different disease conditions in animal studies as well as clinical trials. The antidepressant effects of minocycline have also been documented separately.

**Celecoxib**

Clinical efficacy of AD drugs can be augmented by the addition of selective inhibitor of cyclooxygenase 2 celecoxib. Their antidepressant effect has been described in bipolar patients as well. The proposed mechanism for this beneficial effect has been proposed to be improved antioxidant effect and decreased oxidative stress in hippocampus. A recent meta-analysis has concluded their antidepressant effect to be superior than their side effects profile. However, their use is only recommended in treatment refractory depression due to insufficient number of studies available so far.

**N-acetylcysteine (NAC)**

A strong anti-inflammatory agent, N-Acetylcysteine has been found to increase the efficacy of antidepressant drugs in clinical trials. A useful interaction between NAC and escitalopram in terms of antidepressant activity has been documented. It has been postulated that the antidepressant effect is due to its effects on superoxide dismutase enzyme.

**Statins**

The anti-inflammatory properties of statins make them one of the candidates of adjuvant AD therapy in the future. Statins produced favorable results in trials when administered and compared with fluoxetine. Atorvastatin was found to favorably influence the impact of antidepressants in 12 weeks treatment during compared to antidepressant monotherapy.

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have anti-inflammatory effects in animal models of depression. They have been shown to exert an accelerating effect on the AD therapy in depression. The candidates are Acetylsalicylic acid. These drugs exert their anti-inflammatory effect by blocking the cyclooxygenase (COX) I, II or III, together or selectively. COX is the same enzyme that is involved in the activation of microglia and other immune cells inside the brain. One such study in a day stress model of depression concluded that celecoxib (COX-II Inhibitor) reversed the depressed like behavior and elevation of COX following stress. Although long-term use has been associated with increased gut permeability and other complications, their synergistic effects are nonetheless important enough to suggest future studies into their use as adjuvant to antidepressant therapy in a given episode of depression.
Cytokine Antagonists
Since pro-inflammatory cytokines are increased in depression\(^a\) and a balance in pro and anti-inflammatory cytokines is inclined in favor of pro-inflammatory agents\(^b\)\(^c\), an antagonism of such processes would make a suitable target for AD therapy\(^d\). These agents have been tested in animal models and have been found to be effective to exert antidepressant effect\(^e\). Yet their use in humans has been discouraged because of their serious side effects. Safer and selective inhibitors may be developed in the course of time that may be used safely in humans.

Anti-inflammatory/Neurotrophic cytokines
Contrary to the pro-inflammatory cytokines but not contrary to the logic, anti-inflammatory cytokines have shown important antidepressant like effect. Erthropoietin, for example, has shown to exert antidepressant like effects in forced swim test\(^f\) possibly by ameliorating the functioning of another neurotransmitter cytokine called brain derived neurotrophic factor (BDNF). Many other antidepressant pharmacological and other therapies also involve the improvement in BDNF status for their action\(^g\)\(^h\).

IL-10, which is considered as an anti-inflammatory cytokine, has been found to be decreased in the depressed subjects body. Its replacement/therapy, which restores its levels to normal, also improves the mood symptoms associated with chronic stress\(^i\).

Steroids
Alterations in steroid regulatory mechanism have been documented as the hallmark of depression pathophysiology\(^j\). It is for this reason drugs interfering with steroid concentrations have been implicated in recovery from depression, particularly in treatment resistant cases. Metyrapone, a cortisol synthesis inhibitor, is such an example that is increasingly being used as adjuvant in antidepressant treatment\(^k\). It is because the resistance to treatment is often blamed on endocrine and inflammatory factors\(^l\).

CONCLUSION

Depressive illness has a significant biological component which is represented by the over activation of microglial cells, increase in proinflammatory cytokines in plasma during an episode of depression, alterations in glucocorticoid concentration and regulation as well as predisposition to degenerative diseases. Recognition of these factors in potential subjects may help predict a better treatment plan with possibly the adjunct medicine targeting inflammatory mechanisms. This, on one hand, may reduce the treatment failure with first line treatment options alone. Secondly it may also reduce the cost of illness by bringing an early remission in the symptoms. Further research into the effects of these drugs along with a view of their safety profile would be necessary for future evaluations.

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