

ADJUVANT THERAPY IN DEPRESSION: A REVIEW

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# ABSrnACT



Major depressio11 is a disabling disorder. With ever increasing disease burden andprojected risein disability, it is thefocus of alot of research. Althoughthecurrent first line antidepressant therapy is much better in terms of safety profile than itspredecessors, 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 suggestivealot of innovation in the treatment strategy. These groups include cortisol synthesis inhibitors, microglial activation inhibitors, mechanistic target of rapamycin (mTOR) pathway inhibitors,inhibitors of tryptophan-kyneurininepathway, cortlcotropin releasing factor 1 (CRFl) receptor inhibitors, P2X7 receptor inhibitors and anti-inflammatory agents. Many of these agents are under the process of experimentation for approval tobeused inhumans. Anti· inflammatory agents, however, are many in number and already approved forhuman 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 tothefirstlineantidepressanttherapy.

**N[UROBIOLOGYOr ou• [SSION**

Depression is a costly public health problem that has been given tremendous emphasis in last coupleof decades.Epidemiologicalsurveys 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 (SSRls) has been *very* helpful mainly because of their better safety profile and consequent increase in patient compliance'. Yet the achievementsin terms of rateand sustainabilityof remission have been far from being satisfactory'.If the unpublished studies submitted to Federal Drug Authority (FDA) are accounted for, the antidepressant effect of SSRls *is* marginally better thanplacebo'.This,in part,has been dueto thedeficiency on the understanding of pathophysiological processes involved in depressive illness. On a fundamental note, thus, the underlying difficulties in understanding ofpathophysiologicalprocesses have beenunearthed oneafter theother.Whathasresultedisavery complexandheterogeneous pictureofthe 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 differenttermslikevascular depression•.in additionto various degrees of stress, genetic predispositions, hypothalamo-pituitary-adrenal axis (HPA axis) dysregulatlon, vascular dysfunction, immune activation etc. have been posttJlated to give rise to molecular mechanism like decreased neurogenesis, proliferation and maturation, decreased size of hlppocampus, alterations in neuroplasticity, decreased arterial and brain pulsatility which individually or collectively lead toeventualalterationsin mood•,

Asstated earlier,manymechanisms havebeenproposed to playtheir rolein 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 on10• The data presented in two successive reviews claimed to connect the dots between activation of immune system and induction of depressivesymptoms".This fact has been highlighted especially withthe arrival of pro-Inflammatory drugs like interferon alpha gamma, which is used to boost the inflammatory response, andistypically associated withinductionof depressive symptoms"·".

Theevidence thathas led tothe beliefthat there is aconnection between pro­ inflammatory markers anddepression canbesummarized as follows.

1. An increase in the serum levels of circulating pro-inflammatory cytokines

e.g. lL-1/J;IL-6, and IFN *y* have been observed which corresponds to the severity ofdepressive features and resultlntheacute phaseresponse seen duringdepression""""

1. A depressive-like state has been obseNed in animals as well as humans subjected to pro-inflammatory cytokines therapy such asinterferontherapyin chronicviralhepatitis"



1. Stresslnduced changesin serotonergic andHPA axisactivityare alsoexplainedby Pro-inflammatory cytokineshypothesis"'•·
2. UCMS induces depressive like behavior by the activation of

microglia as well as activation of kyneurinine pathway of serotonin metabolism that may be called as neuroinfla­ mmatlon'·"

1. Newborn neurons are a fragile population sensitive to

i11flammatory changes in the environment as persistently activated inflammatory par.ameters decrease the number of newneuronsand in turnmay possiblyresultintomoodchanges andneurocognitivedecline''

1. incidenceof degenerative diseases of brainishigher amo;1g the subjects previously diagnosed with depfession which possibly mean that a baseline change in inflammatory balance takes placeduring depression which,ifcontinued unabated,resultsin persistent Inflammation anddegeneration'0

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*

Agerelateddepression isincreasingly being recognized asaseparate entity with various different characters.They may include a variable clinical picture, comorbidity with vascular and infiammatory disorders, precipitating factors such as chronic inflammatory conditions, its effect on prognosis of other diseases and an altered responseto first lineantidepressant treatment. So it isbeing named as geriatric depression. Vascular and inflammatory derangements seem to play apivotalrolein deterioration of mental statealongwith age. It is important to look for evidence of these derangements in clinicalprofiles.Itwillhelpestablish thecasefor 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 antidepressanteffect and antidepressanteffectsof"other" medicine in addition to their usual action.

#### *Anti-inflammatory effects of antidepressant(ADJ drugs*

Evidence states that anti-depressant drugs l1elp calm down the inflammatory rage.Themechanisms,however,arehypothesized 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 derangedneuroendocrineaxisamong others.

Fluoxetlne has been found to be effective ln lowering of pro­ inflammatory cytokine levels in blood". VenJafaxine has beenshown

to abolish the neuroendocrine mode of stress cascade" Such findings *have*beenendorsed bymany other studies aswell.

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

Minocycline has also been associated with inhibition of microglial

activation and has been being tested forIts 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 havealsobeendocumented separately".,,

#### *Celecoxib*

Cllnical efficacy of AD drugs can be augmented by the addition of selective inhibitor of cyclopxygenase 2 celecoxib" Their antidepressanteffecthas beendescribed in bipolar patientsas 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 adjuvant antidepressant effect to be superior than their side effects profile". However their use is only recommended in treatment refractory depression dueto insufficient numberof studies available sofar"

#### *N-acetyle cysteine (NAC)*

A strong anti-inflammatory agent. N-Acetyle cysteine has been found to increase the efficacy of antidepressant drugs in clinical trials". A useful interaction between NAC andescitalopram in terms of antidepressant activity has been documented". It has been postulated that the antidepressant effect is due to its effects on superoxidedismutase enzyme"

#### *Stalins*

The anti-inflammatoryproperties 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 duration when comparedto antidepressantmonotherapyY'.

#### *Non-steroidal anti-inflammatorydrugs (NSA/Ds)*

Non-steroidal anti-inflammatory drugs (NSAIDS) have been shown to haveanti-inflammatoryeffects in animal models of depression,.·". They have been shown to exert an accelerating effect on the AD therapy in depression ". The candidates are Acetyi salicylic acid''. These drugs exert their anti-inflammatory effect by blocking the cyclooxygenase (COX) I, II or ill, together or selectively. COX is the sameenzyme that isinvolved in theactivation of microglla andother immunecellsinside thebr;iin••.*One* suchstudyin a'' day stressmodel 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-inflammatorycytokinesareincreased in depression" anda balancein pro and anti-inflammatory cytokines isinclined in favor of pro-ihflammatoryagents""'',anantagonism of suchprocesses would make a suitable target for AD therapy''. These agents have been testedin animalmodels andhavebeenfoundto beeffective to exert antidepressant effect'•. Yet their use in humans has been discouraged because of their serioussideeffects. Safer andselective inhibitors may be developed in the.course of time thatmay be used safely in humans.

## *Anti-inflammatory/Neurotrophiccytokines*

Contrary to the pro-inflammatory cytokines but not contrary to the logic, anti-Inflammatory cytokines have shown important antidepressant like effect. Erythropoietin,for example, has shown to exert antidepressant like effeas in forced swim test49 possibly by ameliorating the functioning of another neurotrophic cytokine called brain derived neurotrophic foctor (BDNF). Many other antidepressantpharmacological andother therapies alsoInvolve the improvement in BDNFstatusfor theiractions'"-''

IL-10,which isconsidered asananti-inflammatorycytokine,has been found to be decreased in the depressed subjects' body. Its replacement/therapy, which restores its levels to normal, also improves themoodsymptomsassociated wtthchronkstress"

## *Steroids*

Alterations in steroidregulatorymechanism have been documented asthehallmarkof depression pathophysiology" ".Itisfor thisreason drugs interfering with steroid concentrations have been implicated in recovery fromdepression,particularlyIn treatment resistant cases. Metyrapone, acortisol synthesis inhibitor,is such an example that is increasingly being used as adjuvant in antidepressant treatment".It is because theresistance to treatment isoftenblamed onendocrine andinflammatory factors".

### CONCLUSION

Depressive illness has a significant biological component which is represented bytheoveractivation of microglial cells,1ncrease in pro­ inflammatory cytokines in plasma during an episode of depression, alterations in glucocorticoidconcentration and regulation as wellas predispositionto degenerative diseases. Recognition of thesefactors 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 safetyprofilewouId benecessary for futureevaluations.

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