



## EFFECT OF ANTIDEPRESSANT TREATMENT ON C-REACTIVE PROTEIN IN DEPRESSION

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ABSTRACT

**Context:** Inflammatory hypothesis of etiology of depression is a growing area of recent research globally.

**Aims:** To study the changes in the levels of C-reactive protein (CRP) in patients with depression before and after antidepressant treatment.

**Settings and Design:** Department of Psychiatry, Sri Manakula Vinayagar Medical College and Hospital, Puducherry over a period of two months.

**Methods and Material:** Cases of depression were recruited based on inclusion and exclusion criteria after obtaining approval from the Institute Ethics Committee. Sociodemographic data was collected using self-designed proforma, Hamilton depression rating scale was used to rate level of depression and clinical diagnosis of depression was made using ICD 10 criteria. The antidepressant treatment was decided by treating psychiatrist. CRP levels were estimated at baseline and three weeks after treatment. Values < 10mg per litre was considered normal.

**Statistical analysis used:** Statistical analysis was done using SPSS version 13. (\*p<0.05)

**Results:** Sample comprised of 36 cases with mean age of 32.38 years ( $\pm 6.3$ ). Psychological stressors were found in 29 cases. Overall HDRS scores were 27.43 ( $\pm 4.05$ ). All cases had received antidepressant medications, venlafaxine hydrochloride (64%), fluoxetine (18%), amitriptyline (18%) and antipsychotic medications, risperidone (66%) and olanzapine (36%) were prescribed for psychotic depression. The mean CRP levels at baseline 1.05 ( $\pm 0.6$ ) was clinically significant after 2 weeks 0.73\* ( $\pm .50$ ).

**Conclusions:** Antidepressant medications decrease CRP levels in cases of depression, favouring the inflammatory hypothesis of depression. Findings were limited by smaller sample size, use of antipsychotic medications, and presence of stress and lack of standardization of laboratory parameters.

### KEYWORDS

antidepressant, inflammation, stress, C reactive protein

### Introduction:

Existing antidepressant treatment options are only effective in about a third to a half of patients.<sup>[1, 2]</sup> Hence, identification of additional pathophysiological pathways involved in depression and its subtypes is needed to guide the development of alternative treatment strategies. Increasing interest has been directed to immune dysregulation in depression. Recently, two meta-analyses have shown that inflammatory marker levels such as C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor alpha (TNF- $\alpha$ ) are increased in depressed persons compared with non-depressed subjects.<sup>[3, 4]</sup> But among these, only studies on antidepressant treatment with Selective Serotonin re-uptake inhibitors (SSRI) have shown consistent associations of CRP with onset and remission of depression.

Depression has been associated with dysregulation of important stress systems of the human body, that is, the hypothalamus-pituitary-adrenal-axis<sup>[5]</sup> and the autonomic nervous system.<sup>[6]</sup> Although the hypothalamus-pituitary-adrenal-axis in normal situations should temper inflammatory reactions, prolonged hyperactivity of the hypothalamus-pituitary-adrenal-axis could result in blunted anti-inflammatory responses to glucocorticoids resulting in increased inflammation. In addition, both decreased parasympathetic as well as increased sympathetic nervous system activity have been associated with increased inflammation. Furthermore, proinflammatory cytokines might inhibit hippocampal neurogenesis, which could lead to a reduced hippocampal volume, which is also seen in depression. Also, several inflammatory markers have been shown to promote indoleamine-2, 3-dioxygenase activation, which catalyzes tryptophan, the precursor of serotonin, to kynurenine, thereby indirectly reducing the availability of serotonin.

A recent systematic review of longitudinal studies had investigated whether raised inflammatory markers indicate an increased risk of subsequent depressive symptoms. Three databases (1970-2012) were searched for longitudinal studies with repeat data on CRP or IL-6 levels and subsequent depressive symptoms. Effect sizes were calculated using a mixed-effects model, with separate meta-analyses for inflammatory markers and age groups. Eight papers

for CRP (14,832 participants) and three for IL-6 (3695 participants) were identified and the results showed a significant association between increased CRP and depressive.<sup>[7]</sup>

Another systematic review assessed the magnitude and direction of associations of depression with C-reactive protein (CRP), interleukin (IL)-1, and IL-6 in community and clinical samples. Articles published between January 1967 and January 2008 in the PubMed and PsycINFO electronic databases were analyzed and the results showed that Each inflammatory marker was positively associated with depression; CRP,  $d = 0.15$  (95% CI = 0.10, 0.21),  $p < .001$ ; IL-6,  $d = 0.25$  (95% CI = 0.18, 0.31),  $p < .001$ ; IL-1,  $d = 0.35$  (95% CI = 0.03, 0.67),  $p = .03$ ; IL-1ra,  $d = 0.25$  (95% CI = 0.04, 0.46),  $p = .02$ . Associations were strongest in clinically depressed patient samples--but were also significant in community-based samples--and when clinical interviews were used. The study concluded that evidence is consistent with three causal pathways: depression to inflammation, inflammation to depression, and bidirectional relationships.<sup>[8]</sup>

Various population and clinical sample based studies have been reported on the possible association between different antidepressants and inflammatory markers such as CRP. Selective serotonin reuptake inhibitors particularly have shown association with decreases in inflammatory markers. In contrast, recent results of two large studies suggest that use of antidepressants, mainly tricyclic antidepressants (TCA), is associated with elevated inflammation levels.<sup>[9]</sup> Another study showed that in newly diagnosed patients of depression, inflammatory markers such as CRP, ESR and WBC count were significantly raised and Selective serotonin reuptake inhibitors SSRIs such as fluoxetine and escitalopram reduced them independent of their antidepressant effect. So, SSRIs have some anti-inflammatory activity independent of their antidepressant action.<sup>[10]</sup> Although numerous studies have been conducted across the globe, research in this interesting topic appears to be scanty from the Indian subcontinent. Hence we planned to conduct this study with the intention to widen the understanding the role of different classes of antidepressants on the inflammatory hypothesis of depression. Our primary objective was to study the changes in the blood levels

of C-reactive protein in patients with depression before and after antidepressant treatment.

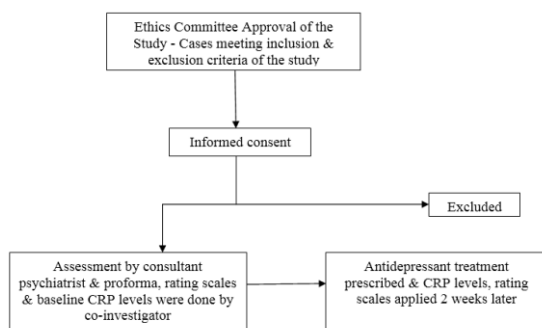
### Materials and Methods:

We designed a Cohort study with before and after treatment evaluation of levels of CRP and cases were selected from the Department of Psychiatry, Sri Manakula Vinayagar Medical College & Hospital, Kalitheerthalkuppam, Puduchery. The study duration was decided as two months (June 6st -July 6th 2014), since as per the yearlong departmental patient statistics, diagnoses of depression was the most common followed by other diagnostic categories. Since there were no similar studies available on this topic from the Indian setting and since the rural setting of our hospital facility was ethnically and geographically variable and hence it was not felt appropriate to make a sample size estimation from any similar study published from outside the Indian subcontinent. Fifty (n=50) patients with depression. Furthermore, the sample size here has been chosen considering the constraints of two months study duration, the number of cases that can be obtained for the study and also on time to be spent by the principal investigator for research work.

**Inclusion criteria:** All patients with depression, both of the unipolar and bipolar type were included into the study although a sincere attempt was made to recruit purely unipolar major depression to minimize the heterogeneity of the sample and the impact of other confounding variables on the study variable. Newly diagnosed patients with major depression or bipolar depression by ICD 10 criteria, of both sexes, between the age ranges of 16–65 years were included into the study.

**Exclusion criteria:** Patients concurrently receiving any other medication that affects the CRP, ESR and WBC levels such as anti-inflammatory drugs and oral contraceptive drugs, patients already receiving antidepressant medications, patients with any infection, e.g., bacterial/viral/fungal/mycobacterial, patients with any allergic complication of infection, such as rheumatic fever, erythema nodosum, those who refused to provide informed consent to participate in the study, and finally those with co-morbid medical conditions such as diabetes mellitus, systemic hypertension, chronic arthritis, bronchial asthma, pulmonary tuberculosis, heart diseases, epilepsy, mental retardation, childhood developmental disorders and other neurodegenerative disorders, formed the exclusion criteria of the study.

**Procedure:** All cases were initially clinically diagnosed by the experienced psychiatrist, based on WHO ICD 10 criteria for depressive disorder. The below flow chart demonstrates the steps involved in recruitment and assessment. Cases were recruited from the psychiatry outpatient and inpatient services of the hospital on a day to day basis based on the above inclusion and exclusion criteria. The informed consent form was translated into the local vernacular Tamil language for the purpose of the study.



**Figure 1: Flowchart of procedure followed in this study**

### Assessment Tools

**Sociodemographic Proforma:** A semi-structured proforma designed for the purpose of the study was used to gather basic sociodemographic data.

**Hamilton Depression Rating Scale:** A clinician-rated scale that measures the severity of, and change in, depressive symptoms in adult population and takes 20-30 minutes to complete was used for this study, mainly since it has been the most widely used depression assessment scale in research. [11] The original version contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week. A score of 0–7 was generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) was usually required for entry into the study. Baseline and post treatment at 2 weeks was done.

**CRP estimation:** Blood levels of CRP was measured at the baseline before starting antidepressant therapy and after 3 weeks of treatment. Normal concentration in healthy human serum has been usually lower than 10 mg/L, slightly increasing with aging. Higher levels have been found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L).

**Quality control:** As a pilot training exercise, the co-investigator who was an undergraduate medical student in his 7<sup>th</sup> Semester, had administered HDRS on 20 patients and then by the treating psychiatrist, and the inter-rater reliability was calculated to be 0.75. Complete confidentiality of all data collected from the participants have been maintained confidentially in the department of psychiatry. This research proposal was approved by the Institute Research and the Ethics Committee (Approval number: 2014-01149)

**Statistical Analysis:** Statistical software for social sciences (SPSS version 13) was used. Sociodemographic variables were analyzed using chi-square for nonparametric variables and student 't' test for parametric variables. Descriptive statistics were calculated for individual scores. 'p' value was set at <0.05.

### Results

At the end of two months, only thirty Six (n=36) cases with major depression could be studied (male: female = 26:10). Mean age was 32.38 years (±6.3). Psychological stressors were found in 29 cases (male: female = 21:7). Overall HDRS scores ranged from 21 to 35 with a mean of 27.43 (± 4.05). ICD-10 diagnoses were as follows, moderate depression without somatic syndrome (n=32%), moderate depression with somatic syndrome (20%), severe depression without psychotic symptoms (13%), severe depression with psychotic symptoms (10%) and recurrent depression (25%). All cases had received antidepressant medications, venlafaxine hydrochloride (64%), fluoxetine (18%), amitriptyline (18%) and those with psychosis received antipsychotic medications, risperidone (66%) and olanzapine (36%). The mean CRP levels at baseline, was clinically significant after 2 weeks post treatment with antidepressants.

**(Table 1)**

**Table 1: CRP levels at baseline and after treatment**

### Discussion:

Our study being the first Indian study to have researched the effect of antidepressant treatment on C-reactive protein levels has yielded clinically significant results. Importantly, antidepressant medications belonging to different chemical groups such as selective serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitor were studied and this is a finding that has not been reported in other studies. Otherwise, the findings of this study concurs with the prevalence characteristics of depression in Indian population in terms of age of presentation and sex difference.

But although the findings of this study tends to offer more support towards predictors of response to antidepressants, it would be of less utility of this evidence if it does not aid in choosing antidepressant medication that would yield the best response. Interestingly, multiple studies across the globe seem to all agree

that the response to various antidepressant medications have been similar and not very different in terms of efficacy.

Moreover, conflicting evidence have been reported that not only tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) but also newer noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine also tends to influence the inflammatory response as part of their pharmacokinetics.<sup>[12]</sup> In addition, reduction in the levels of many inflammatory markers in addition to CRP, such as the Erythrocyte Sedimentation Rate (ESR), and White Cell Count (WCC) has been reported to SSRI treatment.<sup>[10]</sup>

In this context, it might be too early to imprint the exact role of the immune system in the etiology or treatment of depression, placing it under scrutiny.<sup>[13]</sup> Few studies have thrown positive light in supporting the role of these inflammatory agents. From an etiological perspective, the cytokine theory of depressive disorder and its characterisation as a 'psychoneuroimmunological disorder' has already been widely reported.<sup>[13]</sup> Further, from a treatment perspective, both SSRI's<sup>[14]</sup> and mirtazapine<sup>[15]</sup> have been experimented to be found to have clear anti-inflammatory properties.

Although our study has shown positive findings, it is important to take into consideration methodological factors that might have influenced the results namely the presence of psychological stress in majority of our sample. As already evident that stress can make a person vulnerable to depression and can be proinflammatory with causing clinical depression also. Hence it becomes difficult to decipher the baseline elevation of CRP to the presence of stress or because of the severity of depression since there was no correlation of CRP and severity of depression. Another important limitation that could not be overcome was the inclusion of patients with psychotic depression who were treated with antipsychotic medications concurrently. It is well known that this group of medications are pro-inflammatory in nature and this could have further confounded the results of the study. Most studies on this topic have commented on the standardization of CRP levels measured in the study centre and we have not obtained coefficient of variation of CRP levels. Other limitation is that not all antidepressant medications have been tested in this study.

## CONCLUSIONS

The findings of this study does provide useful insights into the research of various antidepressants and their effect on CRP levels, thus enriching existing research knowledge on the inflammatory hypotheses of depression. We speculate that if time constraints could have been overcome, much stringent selection criteria could have been used to refine the sample and such an experiment might probably yield results that could be more meaningful. Studies in future must include the above suggestion and also attempt to study larger sample sizes, non-psychotic depressives, and using standardized laboratory assessment procedures.

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