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EFFICACY OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND EVALUATION OF IL-6, TNF-α AND CRP AS TREATMENT SELECTION BIOMARKERS IN PATIENTS OF DEPRESSION: A SYSTEMATIC REVIEW

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ABSTRACT

Context: Depression is one of the most debilitating illnesses worldwide. As response to available antidepressant treatment takes 4-6 weeks to produce significant clinical response, trying various treatments consume long time before concluding one effective treatment in many patients. Treatment predicting biomarkers to classify groups of patients, can play significantly in monitoring the outcome of their treatment who were given specific class of antidepressant. **Aims:** To find out relationship between baseline level of inflammatory biomarkers (IL-6, TNF-α and CRP) and response of selective serotonin reuptake inhibitors (SSRIs). **Settings and design:** Systematic review **Methods and material:** Literature search on treatment of depression and inflammatory markers was performed in PubMed. Through critical appraisal and screening, 17 out of 387 articles were selected. Statistical analysis was carried out by RevMan 5. **Results:** Efficacy of SSRI was analyzed in 14 studies. Statistically highly significant reduction in HAM-D score was found after treatment with escitalopram [SMD = 9.06 (95% CI: 5.28, 12.83), Z = 4.70, P < 0.00001], sertraline [SMD = 11.70 (95% CI: 8.48, 14.91), Z = 7.13, P < 0.00001] and all SSRIs together [SMD = 10.32 (95% CI: 8.54, 12.09), Z = 11.38, P < 0.00001]. At initiation of SSRI treatment, low baseline level of IL-6 (10 pg/ml), TNF-α (11 pg/ml) and CRP (5 mg/L) were found associated with better clinical outcome in the patients of depression. **Conclusions:** It is evident that SSRIs are effective in treating depression. Low baseline level of IL-6, TNF-α and CRP can predict better response by SSRIs, so baseline level of these biomarkers can be potentially utilized as treatment deciding biomarkers in depressive patients.

KEYWORDS: Antidepressant, Biomarker, SSRI, IL-6, TNF-α, CRP.

INTRODUCTION

Depression is a neurotic disorder and shows various mood symptoms like low mood, sleep disturbance, loss of appetite, etc. It is a very common illness, with more than 264 million people are affected worldwide.[1] In 2015-16, National Mental Health Survey revealed that almost 15% adults in India has mental health issue which needs active intervention and as high as one in twenty Indians suffers from depression.[2] Over last twenty five years, there are growing evidence that in major depressive disorder (MDD) there is immune system activation with derangement in cytokines and acute phase reactant including anti-inflammatory and pro-inflammatory markers.[3,4] Studies show that there is baseline subclinical inflammation in the patients of depression, and inflammation may contribute in etiopathogenesis of depression.[5,6] Evidence shows that levels of proinflammatory markers Interleukin 6 (IL-6) and Tumor necrosis Factor α (TNF-α) and acute phase reactant C-Reactive Protein (CRP) are largely increased in patients of MDD.[7–9] Treatments for depression range from psychosocial to pharmacological and stimulatory including electroconvulsive therapy, transcranial magnetic stimulation and vagus nerve stimulation.[10] In pharmacotherapy, commonly used treatment groups are Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake Inhibitors (SNRI) and Tricyclic Antidepressants (TCA).[10] Either monotherapy from one of these groups or polytherapy from more than one groups is used to treat depression based on severity and response to the treatment.[10] Unfortunately, response to available treatment is highly variable. Some patients of depression respond to SSRIs, while others to TCAs and some does not respond well. Based on clinical examination and history alone, patients cannot be classified into various groups in which either of the available treatment can be said effective. However, there are clinical guidelines for selection of

drug based on clinical features. All antidepressants are almost equally effective, and choice of treatment depends on multiple factors including the safety profile of the drugs.[10,11] It takes 4-6 weeks to produce significant clinical response by any of the currently available major antidepressant drug treatments. As depression is a heterogenous disorder and diagnosis is syndromic, trying various treatments consumes a long period of time before concluding one effective treatment in many patients. So various treatments are needed to be tried over a long period of time till one treatment produces significant clinical response in the patient. Because of this, patient suffering and morbidity remains continuous without significant clinical response over months and in many cases for over years. If we can find some basis to classify group of patients which can be given specific class of antidepressant, patient suffering can be significantly ameliorated. It is a need of time to discover treatment predicting criteria or markers or biomarkers which can be used as treatment decider or predictor and so specific treatment can be chosen for specific patient. SSRIs are currently one of the most used first line treatment due to its favourable side effect profile and tolerability.[10] This study was aimed to find out a relationship between baseline level of peripheral cytokines as biomarker and clinical response of SSRI treatment through evidence based medicine.

MATERIALS AND METHODS

This was a systematic review from the published research articles. After the approval from institutional ethics committee the study was carried out. Methodology was adopted from Cochrane's guidelines for systematic reviews described in Cochrane's Handbook for Systematic Reviews of Interventions by the Cochrane Collaboration with inputs from the book "finding what works in health care: standards for systematic reviews" by Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research[12,13]

Eligibility Criteria: From the online database of MEDLINE - PubMed, full text research articles published in English language, which shows evidence of the effect of SSRIs (escitalopram, sertraline, fluoxetine, and paroxetine) on serum levels of CRP and/or IL-6 and/or TNF-α in depressive patients of either sex with age above 18 years with newly diagnosed and/or who were off treatment for at least 5 half-lives or 3 months were included. Studies published in languages other than English, with closed or paid access to data except articles available through ScienceDirect were excluded. Studies with data of patients who were already on psychotropic treatment, data on effect of anti-depressant drugs other than escitalopram, sertraline, fluoxetine, and paroxetine were also excluded.

Research studies were searched on PubMed using the following search strategy: (SSRI OR Selective Serotonin Reuptake Inhibitor OR Escitalopram OR Fluoxetine OR Sertraline OR Paroxetine OR Fluvoxamine OR Citalopram) AND (CRP OR C-Reactive Protein OR C Reactive Protein OR IL6 OR IL-6 OR Interleukin 6 OR Interleukin-6 OR TNF-α OR TNF α OR TNF-alpha OR TNF alpha OR Tumor necrosis factor α OR tumor necrosis factor alpha) AND (Depression OR Major Depression OR Major Depressive Disorder). As per the inclusion and exclusion criteria, studies were selected to be included in final analysis (Figure 1). Followed by that, studies were critically reviewed and data like demographic details, details of SSRI treatment, details of baseline biomarkers, pre- and post-treatment scores of various depression rating scales like Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), etc.[14–16] were extracted in excel sheet from the included studies.

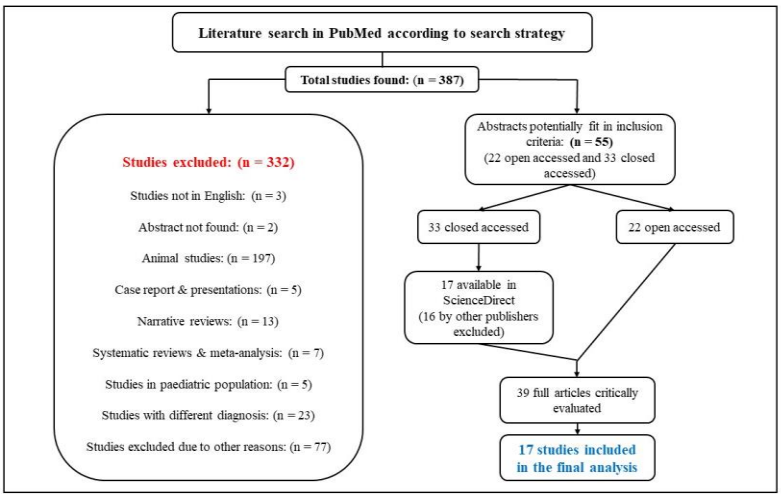


Figure 1: Flowchart of literature search according to inclusion and exclusion criteria.

Statistical Analysis: Data synthesis and evaluation were done through Review Manager (RevMan) 5 software.[17] As different cytokine assays have different sensitivity; comparisons were only made within each study. Most of

the extracted values were in the form of mean ± standard deviation (Mean ± SD), some data were in median ± interquartile range (Median ± IQR). Median ± IQR data were converted into Mean ± SD. Standardized mean difference (SMD) was chosen as the summary statistic for meta-analysis and pooled using the generic inverse variance method in RevMan 5. A random effects model was chosen because included studies were heterogenous with many variations in data. P <0.05 and <0.001 were considered as statistically significant and highly significant respectively. In RevMan 5 with use of funnel plot publication bias was assessed by plotting the effect size against sample size for each study data. From the forest plot of SMD of individual studies, heterogeneity in changes was assessed visually. In RevMan 5 software, statistical estimates of heterogeneity were assessed using the I^2 heterogeneity statistic. To find out baseline level of all three cytokines mean of all means ± SD of pre-treatment values of all biomarkers was calculated for all IL-6 group, all TNF-α group and all CRP group of studies separately. Followed by that mean change in HAM-D was calculated using RevMan in each biomarker group. Then, baseline level of cytokines was compared with mean change in HAM-D score.

RESULTS

A. Demographic details of included studies:

Seventeen studies[8,18–33] were included in this systematic review. From which data of total 843 participants were extracted. Sample size was ranged from minimum 14 to maximum 104. The age range of patients included in these studies was between 18 years and 75 years. Out of 843 participants, 252 were males while 591 were females. Ten out of 17 were Randomized Clinical Trials (RCTs) while rest were non-RCTs.

B. Efficacy of treatment with SSRI based on changes in HAM-D Rating Scale: HAM-D is a rating scale used to check the change in the depressive symptoms in a patient of MDD and so can be used to check the efficacy of the treatment. Six and five of the included studies had measured the effect of escitalopram and sertraline treatment respectively. With the use of the random-effects model, there was statistically highly significant reduction in HAM-D score observed after treatment with escitalopram and sertraline. [Escitalopram: SMD = 9.06 (95% CI: 5.28, 12.83), Z = 4.70, P < 0.00001; Sertraline: SMD = 11.70 (95% CI: 8.48, 14.91), Z = 7.13, P < 0.00001]. There was substantial heterogeneity between the studies found. [Escitalopram: τ^2 = 28.93, χ^2 = 341.90, df = 7, p < 0.00001, I^2 = 98%; Sertraline: τ^2 = 9.18, χ^2 = 26.94, df =3, p < 0.00001, I^2 = 89%] (Figure: 2, 3, 5). Out of seventeen, fourteen studies have measured the effect of SSRIs through various depression rating scales. With the use of the random-effects model, there was statistically highly significant reduction in HAM-D score observed after treatment with various SSRIs. [SMD = 10.32 (95% CI: 8.54, 12.09), Z = 11.38, P < 0.00001]. There was substantial heterogeneity between the studies found. [τ^2 = 13.90, χ^2 = 497.80, df = 17, p < 0.00001, I^2 = 97%] (Figure: 4, 5).

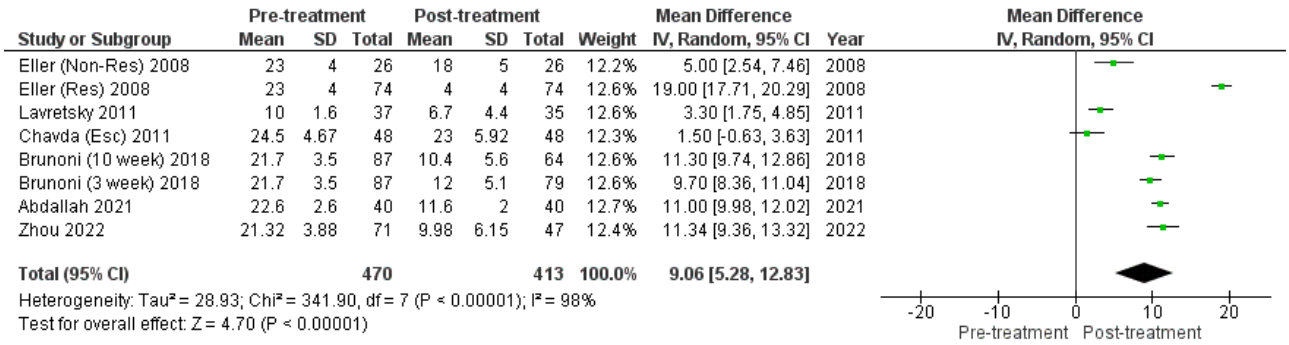


Figure 2: HAM-D score changes after treatment with Escitalopram.

[With the use of the random-effects model, after treatment with escitalopram, statistically highly significant reduction in HAM-D score (P < 0.00001) was observed.]

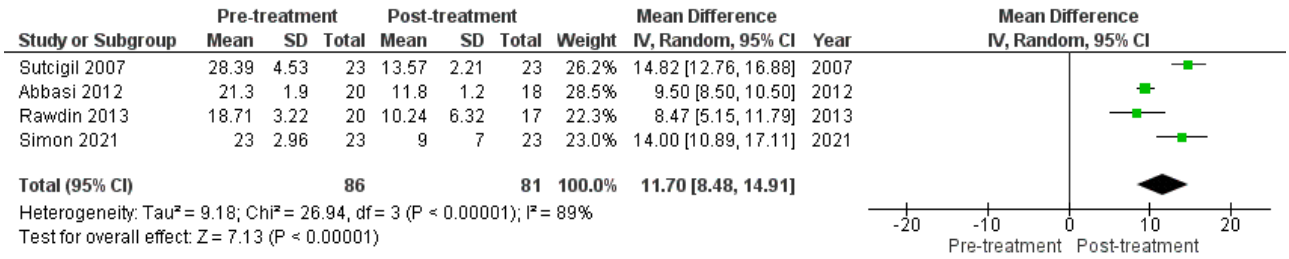


Figure 3: HAM-D score changes after treatment with Sertraline.

[With the use of the random-effects model, after treatment with sertraline, statistically highly significant reduction in HAM-D score (P < 0.00001) was observed.]

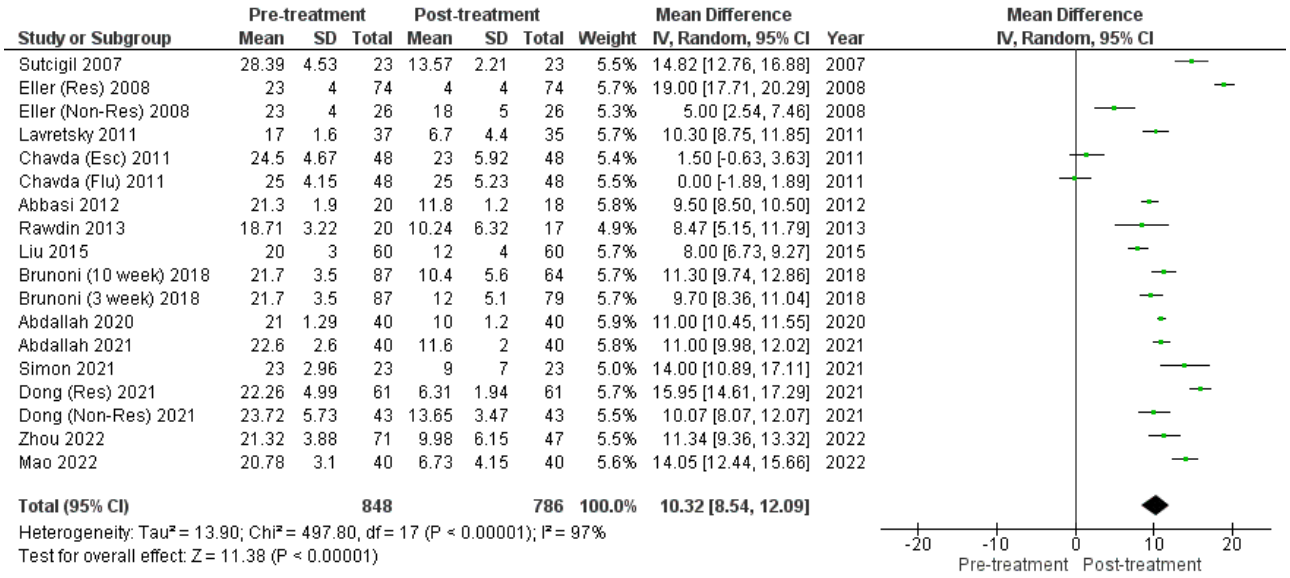
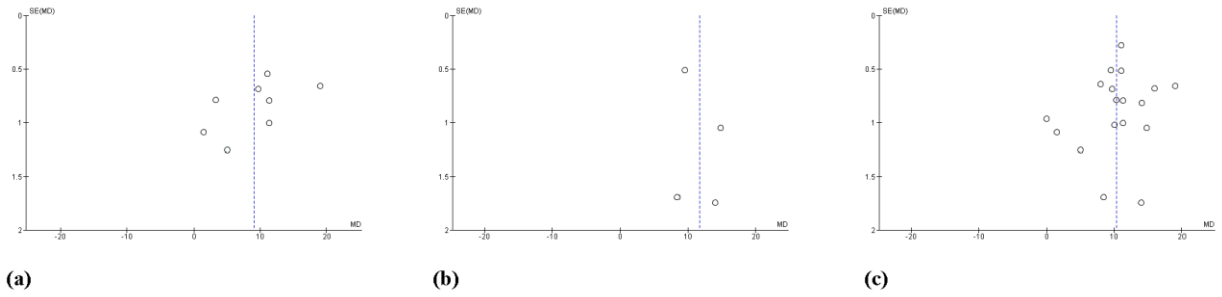


Figure 4: HAM-D score changes after treatment with SSRIs.

[With the use of the random-effects model, after treatment with SSRIs – escitalopram, sertraline, fluoxetine and paroxetine, statistically highly significant reduction in HAM-D score (P < 0.00001) was observed.]



Funnel plot of HAM-D score changes after treatment with Escitalopram (a), Sertraline (b) and all SSRI (c).

Figure 5: Funnel plots of HAM-D score changes after treatment with Escitalopram (a), Sertraline (b) and all SSRI (c).

(A plot of effect estimate in form of standard mean difference against its standard error for a single outcome)
(Funnel plots of HAM-D score changes after treatment with escitalopram, sertraline and all SSRI were visually asymmetric.)

C. Baseline level of inflammatory biomarkers and efficacy of SSRI treatment:

In this evidence based analysis, baseline values of IL-6, TNF-α and CRP were extracted from included 17 studies and were compared with change in HAM-D scores in patients of depression. Changes in the IL-6, TNF-α and CRP were studied in ten, seven and five of the seventeen included studies respectively (Table 1).

Table 1: SSRIs, Biomarkers and HAM-D.

Study name	Biomarker assessed	Antidepressant used	Dose (mg/day)	Duration of treatment	Baseline level of biomarker		
					IL-6 (pg/ml)	TNF-α (pg/ml)	CRP (mg/L)
Brunoni 2018	IL-6	Escitalopram	10	10	3.5 ± 2.30	-	-
Brunoni 2014	IL-6, TNF-α	Sertraline	50	6	1.74 ± 0.07	0.25 ± 0.09	-
Rawdin 2013	IL-6	Sertraline	50-200	8	0.96 ± 0.84	-	-
Lavretsky 2011	CRP	Escitalopram	10-20	10	-	-	2.6 ± 2.3
Zhou 2022	CRP	Escitalopram	10	12	-	-	0.54 ± 0.29
Sutcigil 2007	TNF-α	Sertraline	50-100	8	-	77.68 ± 16.21	-
Mao 2022	CRP, IL-6	SSRI	-	6	28.99 ± 5.51	-	2.92 ± 2.51
Liu 2015	IL-6	SSRI	-	6	6.9 ± 0.8	-	-
Abdallah 2020	CRP, IL-6, TNF-α	Fluoxetine	20	12	9.2 ± 1.28	10.22 ± 1.42	5.08 ± 0.71
Abdallah 2021	TNF-α	Escitalopram	20	6	-	11.12 ± 3.42	-
Simon 2021	TNF-α	Sertraline	-	6	-	0.78 ± 0.6	-
Chavda 2011	CRP	Escitalopram	20	8	-	-	4.04 ± 2.59
		Fluoxetine	20	8	-	-	4.04 ± 2.60
Abbasi 2012	IL-6	Sertraline	200	6	2.78 ± 0.72	-	-
Jazayeri 2009	IL-6	Fluoxetine	20	8	2.12 ± 2.34	-	-
Dong 2021 (Res)	IL-6	Paroxetine	10-40	8	7.87 ± 2.62	-	-
Dong 2021 (Non-Res)	IL-6	Paroxetine	10-40	8	9.95 ± 2.65	-	-
Eller 2008 (Res)	TNF-α	Escitalopram	10-20	12	-	5.70 ± 1.55	-
Eller 2008 (Non-Res)	TNF-α	Escitalopram	10-20	12	-	6.38 ± 2.02	-
Chen 2018	IL-6, TNF-α	Paroxetine	10-40	8	7.15 ± 7.49	15.95 ± 15.43	-

In case of IL-6, the baseline value was varying between 0.96 pg/ml to 28.99 pg/ml. If one study, *Mao et al.*, 2022 with significantly higher level of IL-6 - 28.99 pg/ml compared to other studies was excluded from the analysis, the varying range becomes 0.96 pg/ml to 10.24 pg/ml. The mean baseline level of IL-6 of means of all included studies with IL-6 was 7.6 ± 2.54 pg/ml. In case of TNF-α, the baseline value was varying between 0.25 pg/ml to 77.68 pg/ml. If one study with higher range of 77.68 pg/ml of TNF-α is excluded from analysis the varying range becomes 0.25 pg/ml to 15.95 pg/ml. The mean baseline TNF-α of means of all included studies which has analyzed TNF-α was 14.26 ± 5.09 pg/ml. In case of CRP, the baseline value was varying between 0.54 mg/L to 5.08 mg/L. The mean baseline CRP of means of all included studies which has analyzed CRP was 3.20 ± 1.83 mg/L.

Pre- and post-treatment HAM-D data was available in seven studies in which IL-6 was studied, and five studies each in which TNF-α and CRP were studied. With the use of the random-effect model, there was statistically highly significant reduction in HAM-D score observed in all IL-6 group, TNF-α group and CRP group of studies. [IL-6 group: SMD = 10.97 (95% CI: 9.46, 12.47), Z = 14.29, P < 0.00001; TNF-α group: SMD = 12.50 (95% CI: 9.43, 15.58), Z = 7.97, P < 0.00001; CRP group: SMD = 8.08 (95% CI: 4.36, 11.80), Z = 4.25, P < 0.0001] There was substantial heterogeneity between the studies found. [IL-6 group: $\tau^2 = 4.63$, $\chi^2 = 102.91$, df = 8, p < 0.00001, $I^2 = 92\%$; TNF-α group: $\tau^2 = 13.83$, $\chi^2 = 169.67$, df = 5, p < 0.00001, $I^2 = 97\%$; CRP group: $\tau^2 = 20.89$, $\chi^2 = 207.52$, df = 5, p < 0.00001, $I^2 = 98\%$] (Figure 6, 7, 8, 9).

Overall, based on above analysis, low levels of IL-6 (< 10 pg/ml), TNF-α (< 11 pg/ml) and CRP (<5 mg/L) at baseline in patients of depression were found associated with favourable SSRI treatment response and improvement in the clinical disease.

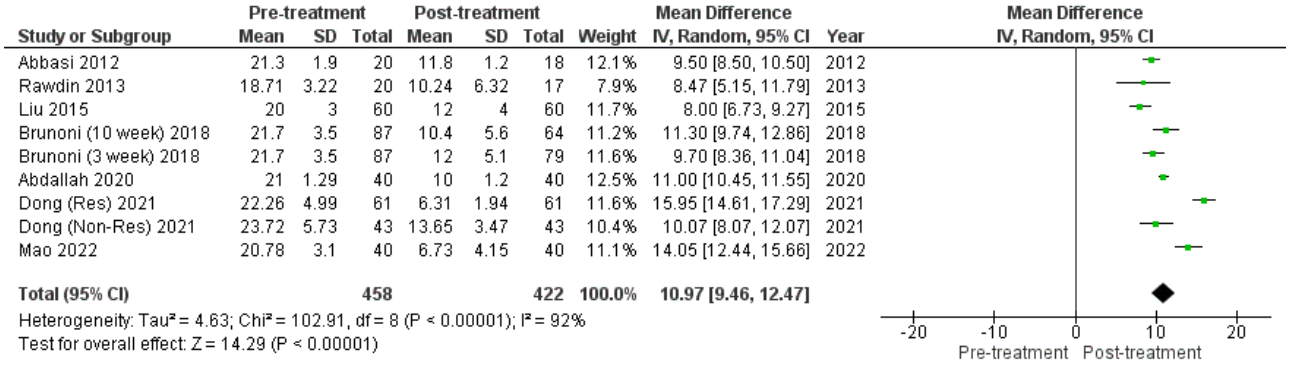


Figure 6: HAM-D score changes after treatment with SSRI in all the studies in which change in IL-6 was tested.

[With the use of the random-effects model, statistically highly significant reduction in HAM-D score ($p < 0.00001$) was observed when pre- and post-treatment HAM-D score was analyzed together in all the studies where change in IL-6 was tested.]

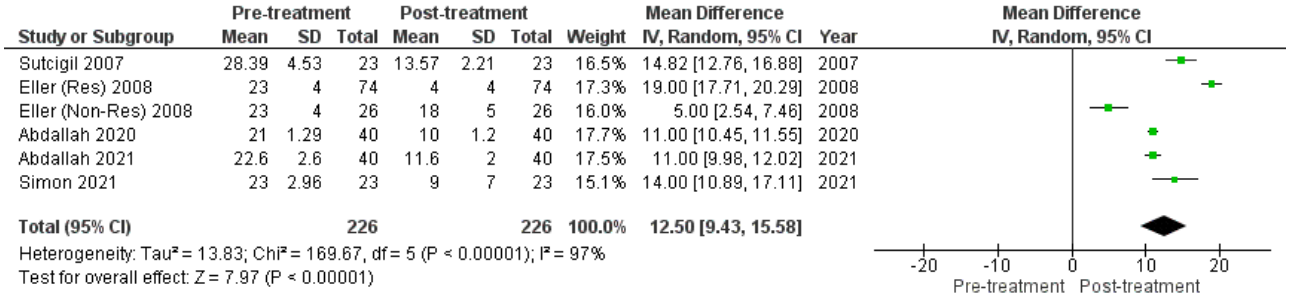


Figure 7: HAM-D score changes after treatment with SSRI in all the studies in which change in TNF-α was tested.

[With the use of the random-effects model, statistically highly significant reduction in HAM-D score ($p < 0.00001$) was observed when pre- and post-treatment HAM-D score was analyzed together in all the studies where change in TNF-α was tested.]

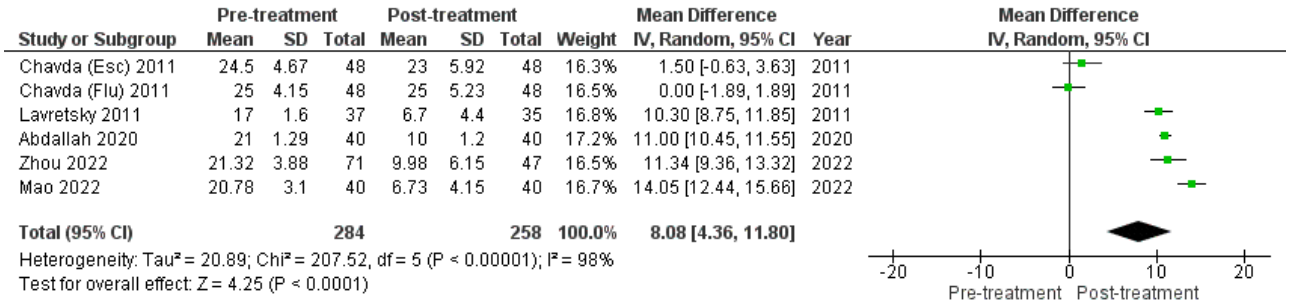


Figure 8: HAM-D score changes after treatment with SSRI in all the studies in which change in CRP was tested.

[With the use of the random-effects model, statistically highly significant reduction in HAM-D score ($p < 0.0001$) was observed when pre- and post-treatment HAM-D score was analyzed together in all the studies where change in CRP was tested.]

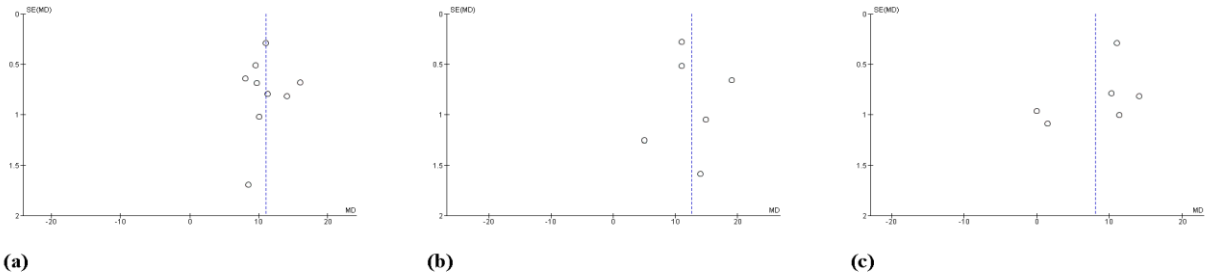


Figure 9: Funnel plot of HAM-D score changes after treatment with SSRI in all the studies in which change in IL-6 (a), TNF-α (b) and CRP (c) was tested.
(A plot of effect estimate in form of standard mean difference against its standard error for a single outcome)
(Funnel plots of HAM-D score changes after treatment with SSRI in all the studies in which change in IL-6, TNF-α and CRP is tested are visually asymmetric.)

DISCUSSION

Since approval of fluoxetine in 1987 till date, various SSRIs like citalopram, escitalopram, sertraline, paroxetine, fluvoxamine and fluoxetine itself are used as the mainstay and first line therapy in the patients of depression.[34] The efficacy of the SSRIs is almost comparable to the efficacy of TCAs, but the SSRIs have significantly less side effects, toxic effects and better tolerability compared to TCAs.[35] A systematic review and a guide to selection of SSRI done by *Edwards et al.*, years back in 1999 showed that fewer patients who were taking SSRIs had discontinued therapy compared to TCAs which is still relevant while selecting treatment of depression in 2022.[36]. Also, TCAs have low therapeutic index and can produce cardiac conduction abnormalities, seizures, etc. with overdose while these effects are unlikely with the use of SSRIs.[37] Due to all these reasons SSRIs are preferred in clinical practice over TCAs. We reanalysed this fact in our study with reference to literatures included as evidence. The efficacy of escitalopram and sertraline individually and all four included SSRIs together based on the changes in the HAM-D scores. HAM-D scale was developed by *Hamilton M* in 1960, afterward various modifications in the scale were done and is currently used in various research to analyse efficacy of antidepressant therapy.[15] In our study, we also analyzed efficacy of SSRI in the pooled data of 17 studies with this widely used HAM-D scale. The results showed that with treatment of escitalopram, sertraline and all four included SSRIs together for duration of 3 ffweeks to 12 weeks, HAM-D score reduces significantly which depicts well known fact that all SSRIs are efficacious in patients of major depressive disorder.

The results also suggested that low baseline blood levels of all three cytokines – IL-6, TNF-α and CRP before the beginning of therapy in patients of depression was associated with good and favourable clinical outcome with significant reduction in HAM-D score.

Similar to what we have found, in systematic review done by *Arteaga-Henríquez et al.*, 2019 and another study by *Yoshimura et al.*, 2009 showed that low baseline levels of proinflammatory cytokines like IL-6 was associated with better response to serotonergic antidepressant treatment while higher level was associated with poor treatment response.[38,39] Contradictory to our results one meta-analysis conducted by *Strawbridge et al.*, in 2015 showed no association between baseline level of IL-6 and treatment response when treated with antidepressant medications.[40]

A systematic review by *Strawbridge et al.*, 2015 which included 35 studies to analyse relationship between cytokines and antidepressant treatment response, and immunomodulatory effect of the treatment showed that high baseline TNF-α levels was associated with poor treatment response and there was no significant change in the level of TNF-α in these resistant patients after treatment while responders showed low baseline cytokine level.[40] Contradictory to our findings, study by *Yoshimura et al.*, in 2009 showed that there was no difference in baseline TNF-α levels in patients with poor treatment outcome and in patients with better outcome.[39]

Similar to result of our evidence based study, one meta-analysis and systematic review by *Arteaga-Henríquez et al.*, published in 2019 showed that baseline low level of pro-inflammatory marker CRP is associated with better treatment response with serotonergic antidepressant drugs like SSRI.[38] Similar type of association between CRP and treatment efficacy was found in studies done by by *Uher et al.*, in 2014, *Jha et al.*, in 2017 and 2019, and *Zhang et al.*, in 2019.[41–44] Contradictory to our result, meta-analysis by *Strawbridge et al.*, published in 2015 showed that there was no association between baseline CRP level and subsequent successful clinical response to antidepressant drug therapy.[40]

CONCLUSION

Based on above analysis, it is evident that SSRIs are effective in treating major depressive disorder. It can be established that low baseline level of IL-6, TNF-α and CRP will predict better response by SSRIs and so, baseline level of these biomarkers can be potentially utilized as treatment deciding biomarkers in the patients of major depressive disorder.

REFERENCES

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study, 2017. The Lancet., 2018; 392(10159): 1789–858.
2. Depression [Internet]. WHO. Available from: https://www.who.int/india/health-topics/depression.
3. Gibney SM, Drexhage HA. Evidence for a dysregulated immune system in the etiology of psychiatric disorders. J Neuroimmune Pharmacol, 2013 Sep; 8(4): 900–20.
4. Müller S, Chang HC, Köhler H. Perturbation of the idiotypic network. I. Induction with multiple alloantigen stimulation. Cell Immunol, 1989 Apr; 119(2): 353–72.
5. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry, 2009 May; 65(9): 732–41.
6. Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep., 2011 Dec; 13(6): 467–75.
7. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry, 2010 Mar; 67(5): 446–57.
8. Mao L, Ren X, Wang X, Tian F. Associations between Autoimmunity and Depression: Serum IL-6 and IL-17 Have Directly Impact on the HAMD Scores in Patients with First-Episode Depressive Disorder. J Immunol Res., 2022; 2022(Mdd): 1–6.
9. Liu Y, Ho RCM, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord, 2012 Aug; 139(3): 230–9.
10. Sadock B, Sadock V, Ruiz P. Kaplan & Sadocks's Comprehensive Textbook of Psychiatry. 10th ed. Philadelphia: Wolter Kluwer; 2017.
11. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. Can J Psychiatry, 2010 Mar; 55(3): 126–35.
12. JPT H, J T, J C, M C, T L, MJ P, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane, 2022. Available from: https://training.cochrane.org/handbook
13. Jill E, Levit L, Alfred B, Sally M, editors. Finding What Works in Health Care: Standards for Systematic Reviews [Internet]. Washington (DC): National Academies Press (US), 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209518/
14. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979 Apr; 134: 382–9.
15. HAMILTON M. A rating scale for depression. J Neurol Neurosurg Psychiatry [Internet], 1960 Feb; 23(1): 56–62. Available from: https://pubmed.ncbi.nlm.nih.gov/14399272
16. BECK AT, WARD CH, MENDELSON M, MOCK J, ERBAUGH J. An Inventory for Measuring Depression. Arch Gen Psychiatry, 1961; 4(6): 561–71.
17. Review manager software (RevMan) [Internet]. London: The Cochrane Collaboration, 2021. Available from: www.cochrane.org
18. Brunoni AR, Padberg F, Vieira ELM, Teixeira AL, Carvalho AF, Lotufo PA, et al. Plasma biomarkers in a placebo-controlled trial comparing tDCS and escitalopram efficacy in major depression. Prog Neuropsychopharmacol Biol Psychiatry [Internet], 2018; 86(June): 211–7. Available from: https://doi.org/10.1016/j.pnpbp.2018.06.003.
19. Brunoni AR, Machado-Vieira R, Zarate CA, Valiengo L, Vieira EL, Benseñor IM, et al. Cytokines plasma levels during antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS): results from a factorial, randomized, controlled trial. Psychopharmacology (Berl), 2014 Apr; 231(7): 1315–23.
20. Rawdin BJ, Mellon SH, Dhabhar FS, Epel ES, Puterman E, Su Y, et al. Dysregulated relationship of inflammation and oxidative stress in major depression. Brain Behav Immun, 2013 Jul; 31: 143–52.
21. Lavretsky H, Alstein LL, Olmstead RE, Ercoli LM, Riparetti-Brown M, Cyr NS, et al. Complementary use of tai chi chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. Am J Geriatr Psychiatry, 2011 Oct; 19(10): 839–50.
22. Zhou J, Zhou J, Sun Z, Feng L, Feng Y, Xiao L, et al. The association of C-reactive protein with responses to escitalopram antidepressant treatment in patients with major depressive disorder. J Affect Disord,2022 Jun; 306: 32–8.
23. Sutcigil L, Oktenli C, Musabak U, Bozkurt A, Cansever A, Uzun O, et al. Pro- and anti-inflammatory cytokine balance in major depression: Effect of sertraline therapy. Clin Dev Immunol, 2007; 2007: 6–11.
24. Abdallah MS, Mosalam EM, Zidan AAA, Elattar KS, Zaki SA, Ramadan AN, et al. The Antidiabetic Metformin as an Adjunct to Antidepressants in

Patients with Major Depressive Disorder: A Proof-of-Concept, Randomized, Double-Blind, Placebo-Controlled Trial. Neurotherapeutics, 2020 Oct; 17(4): 1897–906.
25. Abdallah MS, Ramadan AN, Omara-Reda H, Mansour NO, Elsokary MA, Elsawah HK, et al. Double-blind, randomized, placebo-controlled pilot study of the phosphodiesterase-3 inhibitor cilostazol as an adjunctive to antidepressants in patients with major depressive disorder. CNS Neurosci Ther, 2021 Dec; 27(12): 1540–8.
26. Simon MS, Burger B, Weidinger E, Arteaga-Henríquez G, Zill P, Musil R, et al. Efficacy of Sertraline Plus Placebo or Add-On Celecoxib in Major Depressive Disorder: Macrophage Migration Inhibitory Factor as a Promising Biomarker for Remission After Sertraline—Results From a Randomized Controlled Clinical Trial. Front Psychiatry, 2021; 12(September): 1–11.
27. Chavda N, Kantharia ND, Jaykaran. Effects of fluoxetine and escitalopram on C-reactive protein in patients of depression. J Pharmacol Pharmacother, 2011; 2(1): 11–6.
28. Abbasi SH, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: Randomized double-blind placebo-controlled study. J Affect Disord, 2012; 141(2–3): 308–14.
29. Jazayeri S, Keshavarz SA, Tehrani-Doost M, Djalali M, Hosseini M, Amini H, et al. Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-1beta and interleukin-6 concentrations in patients with major depressive disorder. Psychiatry Res [Internet], 2010; 178(1): 112–5. Available from: http://dx.doi.org/10.1016/j.psychres.2009.04.013
30. Dong Z, Kuang W, Shen X, Tian L. Plasma levels of interleukin-6 and antidepressant response to Paroxetine in Chinese depressive patients. Psychiatry Res [Internet], 2021; 297(May 2020): 113723. Available from: https://doi.org/10.1016/j.psychres.2021.113723
31. Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitaloprsam in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry [Internet], 2008; 32(2): 445–50. Available from: https://www.sciencedirect.com/science/article/pii/S0278584607003442
32. Chen CY, Yeh YW, Kuo SC, Liang CS, Ho PS, Huang CC, et al. Differences in immunomodulatory properties between venlafaxine and paroxetine in patients with major depressive disorder. Psychoneuroendocrinology [Internet], 2018; 87(325): 108–18. Available from: https://doi.org/10.1016/j.psyneuen.2017.10.009
33. Liu Y, Feng H, Mo Y, Gao J, Mao H, Song M, et al. Effect of soothing-liver and nourishing-heart acupuncture on early selective serotonin reuptake inhibitor treatment onset for depressive disorder and related indicators of neuroimmunology: a randomized controlled clinical trial. J Tradit Chin Med, 2015 Oct; 35(5): 507–13.
34. López-Muñoz F, C Á. History of the Discovery of Antidepressant Drugs. 2016. 365–383 p.
35. Anderson IM. SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety, 1998; 7 Suppl 1: 11–7.
36. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs, 1999 Apr; 57(4): 507–33.
37. Feighner JP. Mechanism of action of antidepressant medications. J Clin Psychiatry, 1999; 60 Suppl 4: 3–4.
38. Arteaga-Henríquez G, Simon MS, Burger B, Weidinger E, Wijkhuijs A, Arolt V, et al. Low-Grade Inflammation as a Predictor of Antidepressant and Anti-Inflammatory Therapy Response in MDD Patients: A Systematic Review of the Literature in Combination With an Analysis of Experimental Data Collected in the EU-MOODINFLAME Consortium. Front Psychiatry, 2019; 10: 458.
39. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. Prog Neuropsychopharmacol Biol Psychiatry, 2009 Jun; 33(4): 722–6.
40. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: A meta-analysis. Eur Neuropsychopharmacol, 2015 Oct; 25(10): 1532–43.
41. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry, 2014 Dec; 171(12): 1278–86.
42. Jha MK, Minhajuddin A, Gadad BS, Greer T, Grannemann B, Soyombo A, et al. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. Psychoneuroendocrinology, 2017 Apr; 78: 105–13.
43. Jha M, MH T. No TitlePharmacogenomics and Biomarkers of Depression. Handbook of Experimental Pharmacology, 2019; 101–113.
44. Zhang J, Yue Y, Thapa A, Fang J, Zhao S, Shi W, et al. Baseline serum C-reactive protein levels may predict antidepressant treatment responses in patients with major depressive disorder. J Affect Disord, 2019 May; 250: 432–8.