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Inflammatory markers as predictive factors for selective serotonin reuptake inhibitors (SSRI) antidepressant effect

Marcadores inflamatórios como fatores preditivos para o efeito antidepressivo dos inibidores seletivos da recaptura de serotonina (ISRS)

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ABSTRACT: *Introduction*: Data have supported the influence of inflammation in the pathophysiology of depression and also the influence of depression in the development of a pro-inflammatory state. Major depressive disorder (MDD), the core depressive condition, has selective serotonin reuptake inhibitors (SSRI) as its first line pharmacological treatment. Efforts have been made to identify predictive factors for the responsiveness to SSRI. Therefore, we conducted this review to evaluate the hypothesis that baseline levels of inflammatory markers predict the responsiveness of MDD to SSRI treatment. *Methods*: A search in the PubMed database was made including the keywords ("SSRI" or "sertraline" or "citalopram" or "fluvoxamine" or "escitalopram" or "fluoxetine" or "paroxetine") and ("cytokines" or "CRP" or "TNF" or "inflammatory") and ("major depressive disorder" or "major depression"). *Results*: The search retrieved 245 manuscripts, from which 12 fulfilled our inclusion criteria. The analysis of these manuscripts suggested that high levels of interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α) and c-reactive protein (CRP) at baseline might predict low responsiveness of MDD to SSRI treatment. Confounders such as cognitive impairment, chronicity and severity of depression, melancholic subtype, age and gender were not systematically included in the studies. *Conclusion*: Findings of this review suggest that high levels of pro-inflammatory markers at baseline might predict low responsiveness of MDD to SSRI treatment. Studies with adequate control for confounders are needed.

Keywords: Cytokines; Depression; Inflammation; Serotonin uptake inhibitors; Biomarkers; Predictive value of tests.

RESUMO: A influência da inflamação na fisiopatologia da depressão e o papel da depressão no desenvolvimento de um estado pró-inflamatório têm sido apoiados por diversos estudos. O transtorno depressivo maior (TDM), principal diagnóstico de depressão, tem os inibidores seletivos da recaptação de serotonina (ISRS) como tratamento farmacológico de primeira linha. Esforços têm sido feitos para identificar fatores preditivos da responsividade ao tratamento antidepressivo os ISRS. Portanto, esta revisão tem como objetivo avaliar a hipótese de que níveis basais de marcadores inflamatórios predizem a responsividade do TDM ao tratamento com ISRS. *Métodos*: Pesquisamos o banco de dados PubMed, incluindo as palavras-chave ("ISRS" ou "sertralina" ou "citalopram" ou "fluvoxamina" ou "escitalopram" ou "fluoxetina" ou "paroxetina") e ("citocinas" ou "CRP" ou "TNF" ou "inflamatório") e ("transtorno depressivo maior" ou "depressão maior"). *Resultados*: A pesquisa identificou 245 manuscritos, dos quais 12 satisfizeram os critérios de inclusão e exclusão e foram incluídos nesta revisão. A análise destes manuscritos sugeriu que níveis elevados de interleucina 6 (IL-6), interleucina 1β (IL-1β), fator de necrose tumoral – alfa (TNF-α) e proteína C-reativa (PCR) na avaliação basal podem prever baixa responsividade da depressão ao tratamento com ISRS. Fatores de confusão como deficiência cognitiva, cronicidade e gravidade da depressão, subtipo melancólico, idade e sexo, não foram sistematicamente incluídos nos estudos. *Conclusão:* Os achados desta revisão sugerem que níveis elevados de marcadores pró-inflamatórios na avaliação basal podem predizer baixa responsividade do TDM ao tratamento com ISRS. Estudos com controle adequado para fatores de confusão são necessários.

Descritores: Citocinas; Depressão; Inflamação; Inibidores da captação de serotonina; Biomarcadores; Valor preditivo dos testes.

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INTRODUCTION

The association of a pro-inflammatory state and depression has been reported in the last twenty years[1]. Depressed patients have been reported to have increased serum levels of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), c-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1)[2] and interleukin-2 soluble receptor[3]. Depression and inflammation are currently thought to be pathophysiologically related and a bidirectional relationship has been supported. Inflammation may participate in the pathophysiology of depression[4] and depression may contribute to the development of a pro-inflammatory state[5]. A possible common genetic predisposition for both may not be excluded; an association between mRNA expressions of the serotonin (5-hydroxy- tryptamine) transport protein (5-HTT) and of inflammatory cytokines have been reported[6]; studies investigating this possibility are needed.

It has been proposed that pro-inflammatory cytokines, including IL-6, TNF-α and IL-1β could increase the risk of depression by decreasing serotonin levels, increasing kynurenine, kynurenic acid and quinolinic acid, and activating the hypothalamic-pituitary-adrenal (HPA) axis[3,7]. It is possible that cytokines are able to activate microglial cells leading to a dysfunctional synaptic pruning and consequent disturb in mood circuits[3]. Also, pro-inflammatory cytokines have been related to psychomotor retardation in depressed patients[8]; an association that could be mediated by a possible effect of inflammation in the cortical striatal circuit[9].

Early data have shown an association of treatment resistant depression with increased levels of IL-6[10]. Complementarily, it has been reported that treatment with tricyclic antidepressants was associated with a reduction in the production of TNF-α and IL-1 β[11]. It has also been shown that depressed patients homozygous for the IL-1beta gene -511T, a genetic type associated with increased secretion of IL-1β, had a trend of favorable response to fluoxetine compared to non-homozygous[12]. Considering these data, it is reasonable to hypothesize that the inflammatory profile plays a role in the responsiveness to antidepressant treatment[6]. Supporting this hypothesis, celecoxib, an anti-inflammatory agent, has been shown to improve the antidepressant effect of sertraline[13].

Recently, it has been proposed that serotonergic antidepressants would affect immunity differently from noradrenergic ones[14], suggesting that studies in this area should consider their specificities and not grouping them as a single antidepressant category. Selective serotonin reuptake inhibitors (SSRI) are the first line antidepressants for the treatment of major depressive disorder (MDD)[15] and efforts have been made to predict their optimal prescription[16]. In this line, if baseline levels of inflammatory markers are predictive of responsiveness to antidepressant, one could *a priori* estimate the efficacy of an antidepressant (or class of antidepressant), improving clinical practice's prescription. Consequently, the objective of this review is to investigate whether inflammatory markers at baseline predict the responsiveness of MDD to a SSRI treatment trial.

METHODS

Search Strategy

For the present review, the PubMed database was assessed to search studies that investigate inflammatory markers at baseline that predicted responsiveness of MDD to treatment with SSRI. We included as search terms "SSRI" (i.e. the class of SSRI) and each specific SSRI antidepressant used in clinical practice, so that the search could be more comprehensive and specific. Thus, we used the following keywords: ("SSRI" or "sertraline" or "citalopram" or "fluvoxamine" or "escitalopram" or "fluoxetine" or "paroxetine") and ("cytokines" or "CRP" or "TNF" or "inflammatory") and ("major depressive disorder" or "major depression").

Inclusion Criteria

The inclusion criteria for this review were: measurement of levels of inflammatory markers or their surrogates at baseline; use of SSRI as an antidepressant treatment; use of standardized scale to measure the depressive severity along the treatment; inclusion of an analysis investigating the association between the baseline levels of inflammatory markers and the outcome of depression with the SSRI treatment for more than four weeks; written in English.

RESULTS

The search in the PubMed database provided 245 studies, from which 19 were potentially relevant according to titles and abstracts. The analysis of these manuscripts led to 12 articles that fulfilled our inclusion criteria (Figure 1).

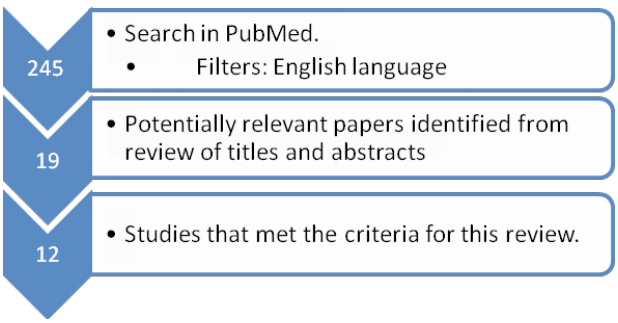

Figure 1: Flow-chart describing the manuscripts' selection process

In the reviewed studies, mean age of patients ranged

from 31 to 50 years old, except for one in which the sample was comprised of children and adolescents aged from 7 to 18 years old[17]. Most studies did not provide a differential analysis for women and men.

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) was the most frequently used criteria to diagnose MDD. Among interviews, the Mini International Neuropsychiatric Interview (MINI) and the semi structured Schedule for Clinical Assessment in Neuropsychiatry (SCAN) were the most used. Most of the studies used more than one instrument to assess severity of depression, including the 17-item Hamilton Depression Rating Scale (HAM-D-17), Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI). The manuscripts exclusion criteria usually included previous history of any major physical disorder; history of schizophrenia, personal or family (first-degree relative) history of mania, major psychiatric disorders, mood-incongruent psychotic symptoms and any major inflammatory disorder immediately preceding the recruitment and pre-treatment.

Baseline inflammatory markers as predictors of antidepressant treatment: focus on specificity of inflammatory markers

C-reactive Protein (CRP)

The only study focusing on CRP reported that its high levels at baseline predicted higher severity of depression after treatment with escitalopram compared to nortriptyline. This study included 115 MDD patients from the Genome-based Therapeutic Drugs for Depression (GENDEP) project[18], a 12-week, open-label pharmacogenetic study, assessing patients with MDD of at least moderate severity according to the ICD-10 or DSM-IV criteria. Sample included European adult men and women with a diagnosis of unipolar, non-psychotic MDD assessed by the SCAN. Subjects were recruited by clinical referrals from primary and secondary care. They included patients with comorbid disorders, severe illness, and suicidal ideation. Sensitivity analyses indicated that inflammatory medical illness, autoimmune conditions, anti-inflammatory medication, smoking and body mass index did not significantly affect the results[18].

IL-1β

High levels of IL-1β predicted lack of response in two of two studies in which it was evaluated[17,19]. In one of the studies, Amitai et al.[17] found that high baseline serum levels of IL-1β predicted non-response after 8 weeks of treatment with fluoxetine. Their sample included 41 children and adolescents aged between 7 and 18 years (mean of 14.1 years); 15 had a diagnosis of MDD, 17 had an anxiety disorder and 9 had both diagnoses according to the DSM-IV criteria. Starting dosage for all patients was 10mg/day for 1 week, and then increased to 20mg/day until week 4; according to the CGI scale on week 5 the dosage could be increased from 20 to 40mg/day. They assessed depression severity using the BDI and the Children's Depression Rating Scale. The endpoint was response to treatment, declared for those who had "much" or "very much" improvement according to the CGI at the end of treatment. Twenty-three subjects (56%) were identified as responders by the CGI[17]. Baseline characteristics including age, gender and body mass index did not differ between responders and non-responders.

The other study, developed by Cattaneo et al.[19], was part of the GENDEP project (see CRP item above). They measured IL-1β mRNA expression in leukocytes at the baseline of a treatment with escitalopram or nortriptyline. They enrolled 38 MDD subjects in the escitalopram arm with mean age of 38.3 years. Response was determined as a decrease of at least 50% on the Montgomery-Asberg Depression Rating Scale from baseline to week 12 of treatment. At baseline, non-responders had significant higher IL-1β mRNA expression compared to responders. Although the analysis was performed for nortriptyline and escitalopram combined, there was no drug *X* response interaction for the association between IL-1β mRNA expression and response to treatment[19].

IL-6

Eight studies investigated the association between baseline IL-6 levels or its genetic surrogates and responsiveness to a SSRI. Association with responsiveness was found in three studies[17,20,21] (Table 1) and no association was found in five[19,22-25]. Among the three studies that found association, low responsiveness to SSRI was associated with higher IL-6 baseline levels in two[17,20] and with lower IL-6 baseline levels in one study[21] (Table 1).

One of the two studies that found an association of nonresponse with high IL-6 baseline levels, from Amitai et al.[17], treated 41 children and adolescents with MDD or anxious disorders for 8 weeks (see details of the study above in the IL-1β item). The other study, from Yoshimura et al.[20], included 51 MDD patients treated with SSRI (paroxetine, n=16; sertraline, n=15; fluvoxamine, n=10) or SNRI (milnacipran, n=10) for 8 weeks. Nonresponse was defined as a decrease smaller than 50% in the HAM-D-17 scores. The nonresponse group treated with SSRI or SNRI had high baseline levels of IL-6. No reference was made regarding an analysis for the SSRI group independently of the SNRI one.

An association of nonresponse with low levels of IL-6 was found by Yoshimura et al.[21] in 118 MDD patients treated with paroxetine (n= 66) or sertraline (n=42) for 8 weeks. Nonresponse was defined as a decrease smaller than 50% in the HAM-D-17 scores from baseline to the week 8. They also found a positive correlation between baseline

plasma IL-6 levels and baseline HAM-D-17 scores. No adjustments for confounders were reported.

Among the five studies that found no association between IL-6 levels and responsiveness to SSRI, two studies[19,25] assessed genetic surrogates and were from the GENDEP project. Powell et al.[26] analyzed the transcription of RNA in the IL-6 target gene in 46 patients (17 male and 29 female) with mean age of 42.6 ± 12.4 years and MADRS mean scores at baseline of 29.8 (± 8.3). Cattaneo et al.[19] assessed leukocyte mRNA expression levels of IL-6 target gene in 38 patients (see item CRP above). The differences in the relative expression of each gene between responders and non-responders were determined using binary logistic regressions, covarying for age, gender, center of treatment and baseline MADRS score in both studies.

One of the other three studies that did not find association of baseline plasma levels of IL-6 and response was developed by Brunoni et al.[22] with 73 depressed patients treated with sertraline or transcranial direct current stimulation. Correlations between MADRS scores and IL-6 levels at baseline were not statistically significant[22]. In the other study, Basterzi et al.[23] did not find an association of lL-6 serum levels at baseline and treatment response measured with HAM-D-17 in 23 MDD patients treated with SSRI.

Table 1. Studies that investigated an association between IL-6 baseline levels and responsiveness to selective serotonin reuptake inhibitor

Authors	SSRI	Sample	Scale	Method	Association between IL-6 baseline levels and responsiveness	Adjustments/covariates/other factors
Yoshimura et al.[20]	Sertraline or paroxetine or fluvoxamine	51 adults MDD	HAM-D-17	Plasma measurement with quantitative sandwich enzyme assay technique, using Quantikine HS High Sensitivity Immunoassay kit	High baseline levels predicted low responsiveness	Reported that baseline levels were high in SSRI-refractory patients, although no separate analysis was shown. Specific adjustments were not mentioned
Yoshimura et al.[21]	Sertraline or paroxetine	118 adults MDD	HAM-D-17	Plasma measurement with quantitative sandwich enzyme assay technique, using Quantikine HS High Sensitivity Immunoassay kit	High baseline levels predicted high responsiveness	Adjustments were not mentioned
Amitai et al.[17]	Fluoxetine	24 children and adolescents MDD or anxiety disorders	CGI-S	Plasma measurement with Sandwich ELISA, based on monoclonal-antibody pair and a biotin-streptavidin amplification system	High baseline levels predicted low responsiveness	Adjustments were not mentioned
Cattaneo et al.[19]	Escitalopram	38 adults MDD	MADRS and HAM-D-17	*GENDEP Gene expression	No association found	Adjustments for age, gender, center of treatment and baseline MADRS
Brunoni et al.[22]	Sertraline	73 adults MDD	MADRS and HAM-D-17	Blood sample, flow cytometry (Cytometric Bead Array Human Th1/Th2/Th17 Kit)	No association found	Adjustments for age, gender, and menopausal status, melancholic depression, atypical depression, obesity (body mass index ≥30 kg/m2) and benzodiazepine use
Basterzi et al.[23]	SSRI	23 adults MDD	HAM-D-17	Plasma measurement with sandwich enzyme assay technique, using Cytelise Human IL-6 kit	No association found	Not mentioned
Manoharan et al.[24]	Fluoxetine	77 adults MDD	HAM-D-17	Plasma measurement with enzyme-linked immunosorbent assay (IL-6 AviBion)	No association found	Not mentioned
Powell et al.[25]	Escitalopram	80 adults MDD	MADRS	*GENDEP, DNA extracted from blood samples	No association found	Covariates: age, sex, center of recruitment, baseline MADRS score and allocated antidepressant drug. Also, previous medication use, duration of depressive disorder and occurrence of a recent stressful life event did not affect the results

MDD: major depressive disorder; CGI: clinical global impression; HAM-D-17: 17-item Hamilton rating scale for depression; MADRS: Montgomery–Åsberg Depression Rating Scale. *GENDEP: Genome-based Therapeutic Drugs for Depression; it was a multicenter project, open-label, randomized; duration: 12 weeks; MDD diagnosis with the semi structured Schedules for Clinical Assessment in Neuropsychiatry interview; primary outcome MADRS; secondary outcome HAM-D-17 and BDI.

IL-11

IL-11 was investigated in two studies using data from the GENDEP project. In one study, Powell et al.[25] explored the potential utility of DNA methylation in IL-11 as a baseline predictor of antidepressant response. In order to achieve that, the analysis included a subset of 113 individuals from the GENDEP project (see CRP item above). Individuals were treated with escitalopram (n = 80) or nortriptyline (n = 33)[25]. The analysis from blood sample of DNA methylation in IL-11 included eleven CpG units. They found that high levels of DNA methylation at CpG unit 4, which determines expression of IL-11, was associated with better response in individuals under escitalopram treatment[25].

Another study of Powell et al.[26] investigated transcriptomic differences between responders and non-responders to escitalopram. Forty-six patients from the GENDEP project under escitalopram treatment were assessed, 25 of them showed a reduction ≥ 50% in the MADRS scores and were considered responders and the 21 remaining were considered non-responders. Transcription of IL-11 at baseline was not different between responders and non-responders.

TNF-α

Our search found five studies assessing the association between responsiveness to SSRI and TNF-α[17,19,20,26,27] (Table 2). Non-response to SSRI was associated with high TNF-α serum levels in two studies[17] and high genetic expression of TNF-α in two studies[19,26]. One study found no association between baseline TNF-α levels and responsiveness to SSRI[20].

Table 2. Studies that investigated an association of TNF-α baseline levels and responsiveness to selective serotonin reuptake inhibitor

Authors	SSRI	Sample	Scale	Method	Prediction according to high baseline levels	Analysis adjustments/ covariates/comments
Eller et al.[27]	Escitalopram	100 adults MDD	MADRS	Enzyme labelled, chemiluminescent sequential immunometric assay	Low responsiveness	Adjustment for age
Powell et al.[26]	Escitalopram	46 adults MDD	MADRS and HAM-D-17	*GENDEP Gene expression	Low responsiveness	Adjustments for age, gender, center of treatment and baseline MADRS
Cattaneo et al.[19]	Escitalopram	38 adults MDD	MADRS and HAM-D-17	*GENDEP Gene expression	Low responsiveness	Adjustments for age, gender, center of treatment and baseline MADRS
Amitai et al.[17]	Fluoxetine	24 children and adolescents MDD or anxiety disorders	CGI-S	Sandwich ELISA, monoclonal antibody pair and a biotin-streptavidin amplification system	Low responsiveness	Adjustments were not mentioned
Yoshimura et al.[20]	Paroxetine, sertraline, fluvoxamine, milnacipran	51 MDD patients	HAM-D-17	Sandwich enzyme assay technique (Quantikine HS High Sensitivity Imunoassay kit)	No correlation found	Adjustments for age, gender, baseline HAM-D-17 score and antidepressant drug

MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; MADRS: Montgomery–Åsberg Depression Rating Scale; HAM-D-17: 17-item Hamilton rating scale for depression.
*GENDEP: Genome-based Therapeutic Drugs for Depression; it was a multicenter project, open-label, randomized; duration: 12 weeks; MDD diagnosis with the semi structured Schedules for Clinical Assessment in Neuropsychiatry interview; primary outcome MADRS; secondary outcome HAM-D-17 and BDI.

The two studies that assessed genetic markers used data from the GENDEP project. The first, published by Cattaneo et al.[19], investigated the association of gene's expressions of glucocorticoid receptor complex, inflammation and neuroplasticity with depression and antidepressant response. One of the objectives of the study was to explore genes expressions at baseline that could predict treatment response to antidepressant treatment. The sample included 74 depressed patients and 34 healthy controls. Patients were assessed at baseline and after 8 weeks of treatment with escitalopram (n =38) or nortriptyline (n = 36). Responders were categorized as those with a reduction of at least 50% in the MADRS score from baseline to the end of treatment. Non-responders had high baseline mRNA levels of TNF-α (+39%). Expression level of TNF-α at baseline was strongly and negatively correlated with response to treatment in the entire group, and also separately for those on escitalopram and those on nortriptyline treatment. The linear regression analysis showed that the best predictive model included TNF-α and two other cytokines (IL-1β) and macrophage inhibiting factor (MIF), both in the overall sample and

separately in the escitalopram-treated group and in the nortriptyline-treated group. In the second study assessing genetic markers, also using data from the GENDEP project, Powell et al.[26] investigated transcriptomic differences between responders and non-responders to escitalopram. They extracted RNA from blood samples of 46 patients treated with escitalopram, 25 were considered responders (i.e. a reduction ≥ 50% in the MADRS scores from the baseline to the end of treatment) and 21 non-responders. Non-responders had higher baseline expression of TNF-α compared to responders.

In one of the two studies assessing TNF-α serum levels, Amitai et al.[17] investigated whether plasma levels of proinflammatory cytokines predicted response to treatment and/or could be altered after fluoxetine treatment in children and adolescents with depression and/or anxiety disorders (see item CRP above). Non-responders had significantly higher TNF-α baseline levels compared to responders.

In the other study assessing TNF-α serum levels, Eller et al.[27] investigated the acute and chronic effects of escitalopram on serum levels of TNF-α and other biomarkers (IL-8 and sIL-2R) in patients with major depression. Blood samples were analyzed with an enzyme labelled, chemiluminescent sequential immunometric assay. The sample consisted of 100 MDD outpatients diagnosed by the DSM-IV criteria using the MINI; severity of depression needed to be at least moderate according to the MADRS (total score of 23 or higher). The study also included a control group of 45 healthy subjects. Patients were treated with escitalopram 10–20 mg/day for 12 weeks. At the end of week 12, patients were defined as responders if the decrease in MADRS total score was at least 50%. They also investigated the influence of baseline inflammatory markers on response and found that non-responders showed higher baseline TNF-α serum levels compared to responders.

No association between baseline TNF-α serum levels and responsiveness to antidepressant was reported by Yoshimura et al.[20]. They enrolled 51 MDD patients diagnosed by the DSM-IV criteria using the MINI; 23 were male and 28 females, with mean age of 40 years. Sixteen patients were treated with paroxetine, 15 with sertraline and 10 with fluvoxamine[20].

Other inflammatory markers

Both sIL-2 and IL-8 were evaluated in one study and no association with responsiveness to SSRI was found[27].

Baseline inflammatory markers as predictors of antidepressant treatment: focus on specificity of each SSRI

Citalopram

One potentially relevant study was obtained from PubMed database search. However, it did not match the criteria of analyzing a possible association between baseline levels of inflammatory cytokines and the responsiveness to citalopram treatment.

Escitalopram

Six potentially relevant studies were obtained from PubMed database considering the titles and abstracts. After evaluating the studies, one was excluded because it did not analyze the possible association between baseline levels of inflammatory markers and outcome of depression with escitalopram treatment. All five studies assessing escitalopram included in this review found that higher inflammatory state at baseline was associated with low responsiveness. Four of the five studies derived from the GENDEP project (Table 3). The study of Uher et al.[18] focused specifically on CRP serum levels and found that high levels of CRP at baseline were associated with poorer response to escitalopram (see CRP item above). Three other studies from the GENDEP project focused on genetic markers. Powell et al.[26], investigated transcriptomic biomarkers for clinical response to escitalopram. They extracted RNA from blood samples of 46 patients, 25 of which were responders and 21 non-responders. They found that TNF expression at baseline was 17% lower in responders compared to non-responders (see item TNF above). They did not find an association of response to escitalopram with baseline relative expression of IL-6 and IL-11. In another study using data from the GENDEP project, Powell et al.[25] investigated DNA methylation, a factor that could affect transcription factor binding, as a predictor of responsiveness to escitalopram. They found that lower levels of DNA methylation in IL-11 at CpG unit 4 were associated with lower responsiveness to escitalopram (i.e. lower decrease in MADRS scores) compared to nortriptyline (i.e. higher decrease in MADRS scores). In a third study from the GENDEP project investigating a genetic marker to predict responsiveness to escitalopram, Cattaneo et al.[19] investigated the leukocyte mRNA expression of genes belonging to inflammation including IL-1α, IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10 and TNF-α in responders and non-responders to escitalopram. Non-responders had higher baseline mRNA gene expression levels of IL-1β, MIF and TNF-α[19].

Eller et al.[27] investigated serum levels of sIL-2, IL-8 and TNF-α (see item TNF-α above). Severity of depression assessed by the MADRS at baseline in responders did not differ from that of non-responders. Responders had lower baseline levels of TNF-α compared to non-responders. No statistically significant differences were found for other cytokines. A significant effect of gender was found. Non-responder males had higher levels of TNF-α than responder males, non-responder females and responder females. Cytokine levels were not influenced by number of depressive episodes nor by melancholic symptoms, although both were significantly high in the non-responder group.

Table 3. Baseline inflammatory markers as predictors of antidepressant treatment: Escitalopram

Authors	Sample	Method	Non-association of baseline levels with responsiveness	Baseline levels association with low responsiveness	Analysis adjustments/covariates/ comments
Eller et al.[27]	100 adults MDD	Multicenter, open-label, randomized, 12 weeks, moderate severity depression by MADRS (23 or higher), diagnosis with DSM-IV and MINI. Blood samples analyzed with enzyme labelled, chemiluminescent sequential immunometric assay	IL-8	High TNF-α and SIL-2R	Cytokine levels were not influenced by number of depressive episodes nor by melancholic symptoms
Powell et al.[26]	46 adults MDD	GENDEP project*, RNA extracted from blood samples and qPCR	IL-6 and IL-11	High expression of TNF-α	Smoking, body mass index and anxiety symptoms did not significantly affect relative expression of TNF-α, IL-11 or IL-6
Cattaneo et al.[19]	38 adults MDD	GENDEP project*, RNA extracted from blood samples	GR, FKBP-4, FKBP-5, IL-1alpha. IL-4, IL-6, IL-7, IL-8, IL-10. BDNF, p11, VGF	High expression of TNF-α, IL-1beta and MIF genes	Study center did not influence treatment response nor were age, gender or baseline MADRS different between responder and non-responders
Powell et al.[25]	80 adults MDD	GENDEP Project*, DNA extracted from blood samples	CpG units 1, 2, 3, 6, 7, 8, 9, 10	Low levels of DNA methylation at CpG unit 4	Previous medication use, duration of depressive disorder and occurrence of a recent stressful life event did not affect the results
Uher et al.[31]	115 adults MDD	GENDEP project*, high-sensitivity immunoturbidimetry assay	Association was found for CRP	High CRP (was the only studied marker)	Smoking, body mass index and anxiety symptoms did not significantly affect the results

MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; MADRS: Montgomery–Åsberg Depression Rating Scale; qPCR: quantitative polymerase chain reaction; CPR: C-reactive Protein.
*GENDEP: Genome-based Therapeutic Drugs for Depression; it was a multicenter project, open-label, randomized; duration: 12 weeks; MDD diagnosis with the semi structured Schedules for Clinical Assessment in Neuropsychiatry interview; primary outcome MADRS; secondary outcome HAM-D-17 and BDI.

Fluoxetine

In our search, considering title and abstract, we obtained five potentially relevant studies focusing on fluoxetine. Reading the studies, three of them did not investigate the relationship between baseline levels of inflammatory markers and responsiveness to antidepressant treatment. Thus, only two manuscripts that assessed fluoxetine were included in this review[17,24]. Amitai et al.[17] measured serum baseline TNF-α, IL-6 and IL-1β in children and adolescents aged between 7 and 18 years old (see IL-1β item above). They found significantly higher levels of all three cytokines in the non-responder compared to the responder group. The study suggests that high levels of these three cytokines may be involved in the refractoriness of antidepressant treatment. The authors concluded that plasma levels of TNF-α, IL-6 and IL-1β could be considered a predictor of responsiveness to SSRI. In this study, measurements were performed with blood samples and all cytokines were assessed with a sandwich ELISA based on a monoclonal- monoclonal antibody pair and a biotin-streptavidin amplification system. Adjustments for confounders were not explored in their results.

The other study investigated the prediction of response to 6 weeks of treatment with fluoxetine according to baseline levels of IL-6 in 73 patients with MDD. IL-6 levels did not differ between responders (n= 39) and non-responders (n=34). IL-6 levels were assessed by ELISA[24].

Fluvoxamine

Only one study investigated the role of fluvoxamine; it found higher baseline IL-6 levels, but not TNF-α, in non-responders compared to responders[20]. Fluvoxamine was analyzed together with paroxetine and sertraline (see below in the paroxetine item)[20].

Paroxetine

Yoshimura et al.[20] investigated whether baseline levels of IL-6 and TNF-α predicted responsiveness to paroxetine (n = 16), sertraline (n = 15) and fluvoxamine (n = 10). The results were reported together for the three SSRI. Baseline IL-6 level, were higher in non-responders than in responders. No correlation was found between TNF-α levels and responsiveness to antidepressant treatment. Yoshimura et al.[21], using sertraline and paroxetine as antidepressants,

found that baseline plasma levels of IL-6 were significantly higher in responders than in non-responders (results were reported together for both SSRI). Additionally, baseline plasma levels of IL-6 showed a tendency to be correlated with the severity of depressive state. No mention was made regarding severity of baseline depression and responsiveness to the antidepressant treatment. Plasma levels of IL-6 were measured with quantitative sandwich enzyme assay technique using a QuantikineR HS High Sensitivity Immunoassay kit.

Sertraline

Six potentially relevant studies with sertraline were found and four met our inclusion and exclusion criteria (Table 4).

In one study, baseline IL-6 levels, but not TNF-α ones, were higher in non-responders than in responders to sertraline. In that study, Yoshimura et al.[21] investigated if baseline levels of IL-6 and TNF-α predicted responsiveness to paroxetine, sertraline and fluvoxamine (see paroxetine item above)[20]. In a posterior study, Yoshimura et al.[21] found that plasma levels of IL-6 were significantly higher in responders than in non-responders using sertraline and paroxetine as antidepressants (see paroxetine above).

Two studies found no association between responsiveness to treatment and baseline levels of inflammatory markers[22,28]. They were conducted with the same sample at the baseline of a randomized double blind clinical trial comparing sertraline to electrical current stimulation. Measured inflammatory markers included IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α. In the study of 2014, Brunoni et al.[22] assessed the cytokines using blood samples and flow cytometry (Cytometric Bead Array Human Th1/Th2/Th17 Kit); whereas in the study of 2015, Brunoni et al.[28] assessed the TNF receptors using a sandwich enzyme-linked immunosorbent assay (ELISA).

Table 4. Baseline inflammatory markers as predictors of antidepressant treatment: Sertraline

Author	SSRI	Sample	Methods	Non-association of baseline levels with responsiveness	Baseline levels association with non-responsiveness	Analysis adjustments/ covariates/comments
Yoshimura et al.[20]	Sertraline and paroxetine	41 adults, MDD	Quantitative sandwich enzyme assay technique, QuantikineR HS High Sensitivity Immunoassay kit	TNF-α	High IL-6 levels	Baseline levels were high in SSRI-refractory patients, although no separated analysis was shown. No adjustment was mentioned
Yoshimura et al.[21]	Sertraline and paroxetine	118 adults, MDD	Quantitative sandwich enzyme assay technique, QuantikineR HS High Sensitivity Immunoassay kit	5-HTTLPR	Lower IL-6 levels	Positive correlation found between patients' baseline plasma IL-6 levels and baseline HAM-D-17 scores
Brunoni et al.[22]	Sertraline	73 adults MDD	Blood sample, flow cytometry (Cytometric Bead Array Human Th1/ Th2/Th17 Kit)	IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α	No association was found	Cytokine plasma levels decreased during treatment (except for TNF- α) regardless of treatment response
Brunoni et al.[28]	Sertraline	73 adults, MDD	Blood sample, sandwich enzyme-linked immunosorbent assay (ELISA)	TNF-α receptors	No association was found	Covariated with therapeutic group (sertraline or tDCS

MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; HAMD: 17-item Hamilton Rating Scale for Depression; MADRS: Montgomery-Åsberg Depression Rating Scale; qPCR: quantitative polymerase chain reaction; CPR: C-reactive Protein; tDCS: transcranial direct current stimulation.

DISCUSSION

In this review, we found some elements supporting the hypothesis that baseline inflammatory markers may predict responsiveness of MDD to a treatment with a SSRI; a relevant field considering the perspective for developing a personalized medicine. However, there are few studies on this subject, some studies have discordant findings, and methodological aspects deserve consideration. We structured the discussion in two approaches: first, focusing on the specificity of each inflammatory marker, then focusing on SSRI as a group and on each SSRI.

Baseline inflammatory markers as predictors of antidepressant treatment: focus on specificity of inflammatory markers

We found that studies have reported prediction of low responsiveness according to high baseline levels of various pro-inflammatory markers including CRP (n= 1 of 1study), IL-1β (n=2 of 2 studies), TNF-α (n=4 of 6 studies), IL-11(n=1 of 2 studies) and IL-6 (n=2 of 7 studies). However, positive findings should be seen in the context of methodologic aspects and all findings, including those that did not find an association and even those that found opposite results.

CRP

The only study focusing on CRP found that high levels at baseline predicted a decrease of 3 points lower on depression severity in those treated with escitalopram compared to those under nortriptyline treatment. The effect size is of clinical significance, and the sample size of 115 subjects is considerable[18]. Of note, such difference between a serotonergic (escitalopram) and a noradrenergic (nortriptyline) antidepressant suggests that the noradrenergic action might be necessary for the efficacy in MDD patients with high inflammatory state at baseline. Considering the ease feasibility of measuring CRP, studies are needed to confirm this suggested low responsiveness to a SSRI in patients with high levels of CRP.

IL-1β

High levels of IL-1β predicted high rate of lack of response in the two studies in which it was evaluated[17,19]. Both studies included a relative small sample size, 38 subjects in the study of Cattaneo et al.[19] and 24 in the study of Amitai et al.[17]. The effect sizes were also relatively small, the baseline levels of IL-1 β (pg/mL) in responders and non-responders were respectively 0.51 (± 0.23) and 0.76 (± 0.40) in the study of Amitai et al.[17]; in the study of Cattaneo et al.[19], non-responders had IL-1β mRNA levels 33% higher than responders. It is worth mentioning that these studies showed convergent results, even though they have distinct characteristics and approaches. First, regarding the assessment of IL-1β, Amitai et al.[17] measured IL-1β serum levels, while Cattaneo et al.[19] measured IL-1β gene expression. The samples were also distinct, Amitai et al.[17] enrolled children and adolescents (mean age of 14.1 years) with diagnosis of MDD or anxiety disorders, while Cattaneo et al.[19] enrolled subjects with mean age of 38.3 years whose only diagnosis was MDD. Response was defined as a reduction of at least 50% in the BDI from baseline to week 12 of treatment in the study of Cattaneo et al.[19], while Amitai et al.[17] defined response based on the Clinical Global Impression scale at the week 8 of treatment. Another difference was the SSRI agent: Amitai et al.[17] used fluoxetine, while Cattaneo et al.[19] used escitalopram.

In summary, although supported by small sample sizes and small effect sizes, these results suggest that increased serum levels or increased gene expression of IL-1β may predict low responsiveness to SSRI treatment. Additionally, this low responsiveness may be extensive for more than one specific SSRI antidepressant, may be extensive for adults, adolescents and children, and may be extensive for MDD and anxiety disorders. Confirmatory studies are required.

IL-6

Among the eight manuscripts studying prediction of response to SSRI by IL-6 baseline levels, high levels predicted low responsiveness in two studies[17,20] and predicted high responsiveness in one study[21], while no association was found in five studies[19,22-25]. In the Amitai et al.[17] study, which found prediction of low responsiveness by high levels of IL-6, the authors emphasize that the treatment group consists of a heterogeneous and small group of children and there might be different neurobiological mechanisms for different phenotypes, which may have confounded their findings. The other study that found that high baseline IL-6 levels predicted low responsiveness was developed by Yoshimura et al.[20]. Intriguingly, in a more recent study from Yoshimura et al.[21] high levels of IL-6 predicted higher responsiveness to a SSRI compared to low levels. This study enrolled 118 subjects, a sample size bigger than the sum of the two studies that found high levels predicting low responsiveness. These data suggest that there might be various factors associated with the relationship between baseline levels of IL-6 and responsiveness to SSRI.

The relevance of IL-6 in depression is enhanced by data showing that increased IL-6 levels has been associated with psychomotor function such as decreased performance on simple and choice movement time tasks[29]. Supporting that high levels of IL-6 denotes a pro-inflammatory state that is associated with low responsiveness to SSRI, O'Brien et al.[30] found that IL-6 levels (not measured in the baseline) were higher in resistant to SSRI treatment depressed patients in comparison to healthy individuals, while those with history of resistance to treatment but currently in remission did not differ from the healthy controls.

In conclusion, although literature data supports a role of IL-6 in depression, findings regarding the prediction of response to SSRI by baseline levels of IL-6 are currently contradictory.

IL-11

Considering the two studies focusing on IL-11, high levels of DNA methylation at CpG unit 4 - that determines expression of IL-11 - was associated with better response to escitalopram in the study of Powell et al.[25], while in the study of Powell et al.[26] there was no association between transcription of IL-11 at baseline and response to escitalopram. Both studies used data from the GENDEP project. Supporting the relevance of IL-11 as a predictor of responsiveness to SSRI, response to escitalopram has been predicted by a single nucleotide polymorphism variant of the IL-11 gene, using a genome-wide association analysis[31], and the gene IL-11 has been associated with inhibition of serotonin signaling[32]. Although the study of Powell et al.[25] assessing methylation, supports the role of IL-11 for predicting response to SSRI, confirmation that peripherally accessed methylation reflects brain tissue changes and the pathophysiological meaning of these changes still deserve investigation. If the role of IL-11 methylation to predict responsiveness of depression to a SSRI is confirmed, studies should investigate the possible determinants of such DNA methylation. In this line, investigating the

association between DNA methylation and characteristics of the depression (i.e. length of depressive episode, psychopathology, length of total period on depression) and recent or early life stressors, could optimize and even personalize antidepressant treatment.

The study of Powell et al.[26] that did not find an association between transcription of the IL-11 target gene and antidepressant response[26] included 46 subjects, while Powell et al.[25] included 80 subjects. Consequently, the smaller sample size may have contributed to the non-detection of the association between transcription of the IL-11 target gene and antidepressant response[26]. The clinical and pathophysiologic relevance of transcription, DNA methylation and IL-11 levels has not been addressed in the studies and deserve consideration in future researches. High methylation decreases the IL-11 expression, suggesting that high levels of IL-11 are associated with low responsiveness to escitalopram[25]; such finding is attenuated by the absence of association found in the study focusing on transcription[26].

TNF-α

Four of the five reviewed studies evaluating TNF-α found that its high levels at baseline were associated with non-response to SSRI treatment. These studies have different methodological aspects. Two of them assessed TNF-α baseline serum levels[17,27], while the other two assessed gene expression levels[19,26]. Additionally, one study addressed the use of fluoxetine in children and adolescents[17], while the three others studies used escitalopram in adults[19,26,27]. Depression severity and improvement and response were assessed with different scales in the studies. Such diversity of approaches with similar results enhance the consistency of findings. Reinforcing the relevance of TNF-α, three of the four studies[19,26,27] performed statistical adjustments for age and gender. Also, patients with anxiety disorder were also included in one study, thus it is possible that the relationship of TNF-α with treatment response may not be restricted to depression. The sample sizes of the studies that found a predictive effect were 24 subject in the study of Amitai et al.[17], 38 in the study of Cattaneo et al.[19], 100 in the study of Eller et al.[27], and 46 in the study of Powell et al.[26]. However, the studies of Cattaneo et al.[19], Powell et al.[26] selected subjects from the same project, the GENDEP, which indicates that these two studies might have similarities that limit considering their results as findings of two independent studies.

Supporting its role for the responsiveness of depression to antidepressant treatment, TNF-α has been associated with increase in the serotonin transporter availability[33] and inhibition of hippocampal neurogenesis[34]. Both effects may potentially explain the low responsiveness to SSRI in patients with increased baseline TNF-α levels.

In conclusion, findings of this review suggested that high levels of TNF-α at baseline may be a marker of low responsiveness of depression to SSRI.

Baseline inflammatory markers as predictors of antidepressant treatment: focus on SSRI as a group

Twelve manuscripts investigated the prediction of responsiveness of depression to SSRI by levels of inflammatory markers at baseline. Among them, seven found an association of low responsiveness of depression to SSRI with high baseline levels of at least one pro-inflammatory marker; eight found no association between responsiveness to SSRI and baseline levels of least one pro-inflammatory marker; and one found an association of low responsiveness with low baseline levels of at least one pro-inflammatory marker. From the twelve manuscripts, three found association of low responsiveness with high levels of all the investigated pro-inflammatory markers; three found non-association of responsiveness of depression to SSRI for all the investigated markers and one found association of low levels of inflammatory levels with low responsiveness for all the investigated markers. It should be noted that among the studies that found non-association for all the investigated markers, two manuscripts were from the same sample[22,28], while all manuscripts that found an association of low responsiveness with high levels of all the investigated pro-inflammatory markers were from different samples. These data, focusing on SSRI as a group, give some support to the hypothesis that high levels of pro-inflammatory markers at baseline might predict low responsiveness do SSRI. Although non-association with at least one marker was reported in most studies, it might be result of a low power of the studies. Additionally, only one study found association of low responsiveness with low baseline levels of pro-inflammatory markers.

Focus on specificity of each SSRI

Five from the five included studies reported low responsiveness to escitalopram predicted by a high baseline pro-inflammatory state assessed by CRP (GENDEP project)[18], TNF expression (GENDEP project)[26]; low levels of DNA methylation in IL-11 at CpG unit 4 (GENDEP project)[25], high baseline mRNA gene expression levels of IL-1beta, MIF and TNF-α (GENDEP project)[19]; and high levels of TNF-α[27]. Among the studies that used sertraline, high baseline levels of pro-inflammatory markers predicted low responsiveness in one study. For fluoxetine, one from two manuscripts reported low responsiveness by high levels of inflammatory markers (i.e. TNF-α, IL-6 and IL-1β)[17] to fluvoxamine in one manuscript (i.e. high baseline IL-6 levels).

Escitalopram

Escitalopram was the SSRI with higher number of manuscripts (n=5) investigating the prediction of its treatment with a pro-inflammatory marker at baseline. Manuscripts reported that a baseline pro-inflammatory state

assessed by high levels of CRP, TNF-α, IL-1b, or IL-11, predicted low responsiveness to escitalopram. It should be noted that four from these five manuscripts used data from the GENDEP project. The findings from the GENDEP project supported that lack of response to escitalopram may be predicted at baseline by direct measure of circulating inflammatory markers such as high levels of TNF-α or its genetic surrogates such as TNF-α mRNA expression[26]. Data with escitalopram also suggested a gender effect, non-responder males had higher level of TNF-α than responder males, non-responder females and responder females. As mentioned above, considering that four manuscripts were from the GENDEP, an overlap in samples from these manuscripts restricts their support as independent studies.

Sertraline

After escitalopram, sertraline was the second SSRI most frequently studied (n=4 studies). One of the four studies showed association between response to sertraline and high baseline inflammatory levels of IL-6[21] (see comments bellow together with paroxetine). In an early study, Yoshimura et al.[20] had found that increased levels of IL-6 predicted non-response to sertraline (analyzed together with paroxetine and fluvoxamine). One limitation in the studies of Yoshimura et al. for the current review is that the analysis was combined for the SSRI. The other two studies were conducted with the same sample[22,28] and they found no correlation between baseline plasma levels of IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α and response to sertraline treatment. Thus, one limitation of these two studies for the current review is that sertraline was analyzed together with electrical stimulation, thus, it is not possible to exclude that an analysis exclusively with sertraline could bring different results. The results of this review are inconclusive for the relationship between the inflammatory state at baseline and responsiveness to sertraline.

Fluoxetine

Regarding fluoxetine, the data suggesting that increased baseline levels of pro-inflammatory markers (i.e. TNF-α, IL-6 and IL-1β) may possibly predict low responsiveness is based in one study[17], while the other found no association.

Paroxetine

For paroxetine, the two studies reported contradictory findings and the studies did not present a separate analysis for paroxetine.

In conclusion, considering SSRI individually the suggestion for a prediction has been reported for escitalopram and fluoxetine. These findings are driven by the scarce number of studies. Head to head comparisons and a significant number of studies are necessary to make any conclusion on this aspect.

Study Limitations

With some exceptions, studies frequently do not valorize the effect. The absence of reporting standardized indicators of effect size restricts a review without meta-analysis like ours. Various manuscripts used samples from the same project, which restricted considering them as independent.

There was also scarce information in most studies concerning variables that may potentially interfere in the relationship between the inflammatory markers at baseline and the antidepressant effect. Therefore, this review could be enriched if the manuscript's statistical analysis were controlled for gender, melancholic/atypical features, chronicity, severity, responsiveness to previous treatment and the presence of cognitive dysfunction.

Perspective for future studies

We recommend that future studies include standardized indicators of effect size. We also recommend the inclusion of variables such as gender, melancholic/atypical features, chronicity, severity, responsiveness to previous treatment and the presence of cognitive dysfunction in appropriated statistical analysis models.

If confirmed, the association of high baseline inflammatory markers with low responsiveness to SSRI supports the investigation of alternative strategies for these patients including the possible augmentation strategies targeting the reduction of such inflammation.

CONCLUSIONS

The results of this qualitative review suggest that baseline markers indicating a pro-inflammatory state may predict low responsiveness of MDD to SSRI treatment. The findings are more supportive for TNF-α and IL-1β, but there are also support for IL-6 and CRP markers. Confirmatory studies are needed, in particularly, studies including adjustment for confounders such as cognitive impairment, chronicity and severity of depression, melancholic subtype, age and gender. Data were insufficient to make inference regarding responsiveness to a specific SSRI.

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