



# The effect of proinflammatory cytokines in Cognitive Behavioral Therapy



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## ABSTRACT

Major depressive disorder (MDD) is a debilitating disorder and its pathophysiology is associated with deregulation of the immune system. We investigated the changes in circulating levels of proinflammatory cytokines (specifically IL-6 and TNF- $\alpha$ ) measured by the ELISA kit in two psychotherapeutic interventions for MDD: Narrative Cognitive Therapy (NCT) and Cognitive Behavioral Therapy (CBT). This is a randomized clinical trial including 97 individuals (18 to 29 years-old) with MDD. In CBT there was a significant difference in serum levels of IL-6 and TNF- $\alpha$ , therefore indicating that CBT was more effective than NCT on serum levels proinflammatory cytokines.

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## 1. Introduction

Major depressive disorder (MDD) is a debilitating disorder with a lifetime prevalence ranging from 10% to 15% (Luca et al., 2013). The pathogenesis of this disorder is not completely understood, however studies have suggested that deregulation of the immune system, particularly the inflammatory cytokines, is associated with the pathophysiology of depression (Blume et al., 2011; Dowlati et al., 2010).

Cytokines are polypeptides with immunoregulating and modulating functions of the neural system (Wang et al., 2002). Proinflammatory cytokines, such as the Interleukin-6 (IL-6) and the Tumor Necrosis Factor alpha (TNF- $\alpha$ ), play important roles in the central nervous system, including synaptogenesis and neuronal plasticity (Kim et al., 2013; Maes et al., 2012). Studies have suggested that depressed patients show increased levels of proinflammatory cytokines (Munzer et al., 2013; Schiepers et al., 2005). Furthermore, this increase seems to be correlated to the severity of this psychiatric disorder (Maes et al., 2012; Schiepers et al., 2005).

Pharmacological treatments act on modulating cytokine production, decreasing its levels (Hannestad et al., 2011; Munzer et al., 2013). However, little is known about the effect of psychotherapy in reducing these levels. Cognitive Behavioral Therapy (CBT) has been effective

in improving depressive symptoms (Butler et al., 2006), but few studies have showed changes in inflammatory parameters after non-pharmacological interventions (e.g., hypnosis, relaxation, mindfulness-based and cognitive-behavioral training) (Keri et al., 2014). The aim of this study was to determine whether psychotherapeutic interventions for MDD are associated with changes in circulating levels of inflammatory cytokines, specifically IL-6 and TNF- $\alpha$ .

## 2. Methods

### 2.1. Design

This is a randomized clinical trial that assesses the effectiveness of brief psychotherapy models in the regulation of pro-inflammatory markers in remission of the depressive symptoms. A convenience sample was recruited through advertisements at Community Health Centers and local media.

### 2.2. Participants

Evaluations were conducted at baseline and post-intervention. Inclusion criteria for participating in the study were: (a) age range of 18–29 years, and (b) depression disorder diagnosed according to the Structured Clinical Interview for DSM-IV (SCID). SCID translation and adaptation to Portuguese showed good reliability, with Kappa coefficient of 0.87 for mood disorders (Del-Ben et al., 1996). Exclusion criteria were: (a) current psychological or psychiatric treatment; (b) current moderate/severe suicide risk; (c) current use of psychoactive substances (except for tobacco and alcohol); and (d) bipolar depression.

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The participants were informed about the research objectives and signed a “Term of Free and Informed Consent”. In this research protocol, all ethical procedures established by the National Health Council, Resolution number 196, October of 1996, were followed. The project was approved by the ethical committee of the university, protocol number 2009/24.

### 2.3. Interventions

The handbook of Cognitive Behavioral Therapy (CBT) was structured in agreement with Aaron Beck's theory (Beck, 1997). This model of psychotherapy proposes that the distorted or dysfunctional thinking which influences mood and behavior is common to all psychological disorders. An accurate assessment and modification in thinking lead to improvements in mood and behavior. Lasting improvements result from the modification of the basic dysfunctional beliefs.

The Handbook of Narrative Cognitive Therapy (NCT) was established according to the proposition of Oscar Gonçalves (1998), from the University of Minho (Portugal) (Gonçalves, 1998). This model aims to reframe personal narratives by elaborating a new biography based on life stories that lost meaning and became incoherent. The new narratives and interpretations are integrated into the personal stories in a coherent and meaningful way.

Both interventions were performed for seven weekly sessions (one session a week) with one hour of duration, at the Hospital Universitário São Francisco de Paula (HUSFP). The sessions were conducted by undergraduate students in the last year of Psychology from the Universidade Católica de Pelotas (UCPel). All students received two months of training and were weekly supervised by senior psychologists.

### 2.4. Data collection

Participants were evaluated regarding sociodemographic data (gender, age, and years of education). Economic status was measured using the National Economic Index (NEI), an instrument that was developed using as main component the analysis that considered the Brazilian census of 2000 as a parameter. The instrument is based on the individual's material assets and the education level of the head of the household (Barros and Victora, 2005).

### 2.5. Outcome measures

The Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) was used to measure the severity of depressive symptoms at baseline and post-intervention.

### 2.6. Biochemical analyses

For the biochemical analyses, 10 mL of blood were withdrawn from each subject by venipuncture into an anticoagulant-free vacuum tube at baseline and post-intervention. All venous blood samples were taken in the morning (between 9:00 and 11:00 am). The blood was immediately centrifuged at 4000 ×g for 10 min, and serum was kept frozen at –80 °C until analysis. Serum IL-6 and TNF-α levels were measured using a commercial immunoassay kit (DuoSet ELISA Development, R&D Systems, Inc., USA). Serum IL-6 and TNF-α levels were expressed in pg/mL.

### 2.7. Randomization

The randomization was performed by a person who was not involved in the evaluation process or the therapeutic intervention; this same person raffled papers from a brown envelope with the indication of the therapy model. Subjects who met the inclusion criteria were

randomized between the two models of brief interventions: NCT and CBT.

### 2.8. Blinding

The researchers who were responsible for baseline and post-intervention assessments and the participants were blinded regarding the intervention model.

### 2.9. Statistical analysis

Statistical analysis was conducted in the SPSS 21.0 software. Chi-square and t tests were used to assess data homogeneity between the intervention models at baseline. Serum IL-6 and TNF-α levels had non-Gaussian distributions. For nonparametric data, we used Wilcoxon test. Serum cytokines levels were presented using median and interquartile range. Results with p value ≤ 0.05 were considered statistically significant.

## 3. Results

We initially assessed 282 subjects. From these, a total of 162 subjects did not meet the inclusion criteria, which resulted in 120 participants (60 NCT and 60 CBT); 23 subjects (NCT = 9 and CBT = 14) were excluded from our sample after scheduling the first session and not attending it for three times. We analyzed data from 97 participants (51 NCT and 46 CBT) at baseline.

During the intervention period, 23 participants (NCT = 12 and CBT = 11) dropped out from the treatment reporting lack of time as the main reason. The participants who presented suicide risk throughout the intervention (NCT = 1 and CBT = 5) were excluded from the study. They received psychological treatment and medication, and their family was informed about the suicide risk. Therefore, 68 participants (NCT = 38 and CBT = 30) completed the therapy and participated in the final assessment. Nevertheless, two blood samples from the CBT model could not be included in the analysis due to hemolization.

There was no significant difference between sociodemographic variables and the therapy models. The average age was 23.89 ± 3.18 and 24.46 ± 3.61 in NCT and CBT, respectively. Also, 81.6% of the NCT participants and 75% of the CBT participants are female. Moreover, there was no difference in the severity of depressive symptoms between therapy models (Table 1).

Severity of depressive symptoms was significantly different from baseline to post-intervention (p < 0.001) in NCT, whereas there was no significant difference in the serum levels of IL-6 (p = 0.987) and TNF-α (p = 0.651) in this same intervention (Table 1). Regarding the CBT intervention, there was a significant difference on the severity of depressive symptoms (p < 0.001), as well as in the serum levels of

**Table 1**  
Baseline demographic and clinical characteristics of each group.

Characteristics	NCT	CBT	p value
Gender <sup>a</sup>			0.521
Female	31 (81.6%)	21 (75%)	
Male	7 (18.4%)	7 (25%)	
Age (years) <sup>b</sup>	23.89 ± 3.18	24.46 ± 3.61	0.508
Scholarity (years) <sup>b</sup>	12.71 ± 3.05	12.59 ± 2.91	0.883
Brazilian Economic index <sup>a</sup>			0.801
1 (Minor)	12 (31.6%)	9 (33.3%)	
2 (Middle)	12 (31.6%)	9 (33.3%)	
3 (Highest)	14 (36.8%)	9 (33.3%)	
HDRS <sup>b</sup>	38 (12.4%)	28 (11.6%)	0.322

Legend: NCT = Narrative Cognitive Therapy; CBT = Cognitive Behavioral Therapy; HDRS = Hamilton Depressive Rating Scale.

<sup>a</sup> Analysis by  $\chi^2$  test.

<sup>b</sup> Analysis by -t test.

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