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Pro-inflammatory cytokines and psychotherapy in depression: Results from a randomized clinical trial

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ABSTRACT

Depression is a serious condition that is associated with great psychic suffering and major impairments on the patient's general health, quality of life, and social and occupational activities. In some cases, it may lead to suicide. Regardless of the innumerous research works that have already addressed depression in wide and specific facets, there is still a lot to grasp in order to effectively help preventing and treating depression. This work presents data from a randomized clinical trial that sought to evaluate the effectiveness of two brief psychotherapeutic for Depression: Cognitive Behavioral Therapy (CBT) and Supportive-Expressive Dynamic Psychotherapy (SEDP). This was a convenience sample composed of 46 individuals that were evaluated using a structured diagnostic interview and then randomly allocated to the SEDP group. We examined baseline and post-intervention serum levels of the Interleukin-6 (IL-6) and the Tumor Necrosis Factor (TNF-α) in addition to the severity of depressive symptoms according to the Outcome Questionnaire - 45.2 (OQ-45.2) and the Beck Depression Inventory (BDI). Results show that serum IL-6 and TNF-α levels, as well as the scores from the OQ-45.2 and the BDI significantly decreased after 16 sessions of SEDP ($p < 0.001$), except for the Interpersonal Relationship domain from the OQ-45. Despite the reduction of serum cytokines levels and OQ-45 and BDI scores, they were only significantly correlated regarding the social role domain from the OQ-45. Nonetheless, our data suggests an effective role of brief psychodynamic psychotherapy in the reduction of depressive symptoms and serum inflammatory levels that are associated with depression.

1. Introduction

Depression is a common mental disorder that often starts at a young age, reduces people's functioning, it is often recurring, and can lead to suicide (WFMH, 2012). The World Federation for Mental Health states that Depression is estimated to affect 350 million people and lifetime prevalence rates range from approximately 3 percent in Japan to 16.9 percent in the United States, with most countries falling somewhere between 8 and 12 percent. Moreover, unipolar depressive disorders will be the leading cause of the global burden of disease by 2030 (WFMH, 2012). Population-based studies in Brazil found a general prevalence of depression of 17–20% (Andrade et al., 2012; Munhoz, 2012), while the prevalence found in clinical samples ranges from 22% to 47% (Fleck et al., 2003; Molina et al., 2012).

The nature and etiology of depression is subject of divided opinion regarding psychogenic and biological causes (Beck and

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Alford, 2009; Maes et al., 1995). Several investigations have demonstrated an association between inflammatory processes and major depressive disorder (Dantzer et al., 2008; Neto et al., 2011; Rot et al., 2009; Schneider and Prvulovic, 2013). In fact, several clinical studies and animal models pointed that inflammation increases the risk of occurrence of major depressive episodes (Bayramgürler et al., 2013; Dantzer, O'Connor, 2008; Heesch et al., 2013; Maes et al., 1995) even though the causal relation between them is still unclear.

Pro-inflammatory cytokines, such as the Interleukin-6 (IL-6) and the Tumor Necrosis Factor (TNF-α) may represent the key factor in the (central) mediation of the behavioral, neuroendocrine and neurochemical features of depressive disorders (Schiepers et al., 2005). They coordinate the local and systemic inflammatory response to microbial pathogens and act on the brain to cause behavioral symptoms of sickness, such as sleepiness, fatigue, loss of appetite and decreased libido (Berthold-Losleben and Himmerich, 2008; Dantzer, O'Connor, 2008). These symptoms have been described as "sickness behavior" and are related to the behavioral changes of depression (Berthold-Losleben and Himmerich, 2008). It is possible that depression represents a maladaptive version of cytokine-induced sickness, which could occur when activation of the innate immune response is exacerbated in intensity and/or duration, or that takes place in the context of an increased vulnerability to depression (Dantzer, O'Connor, 2008).

Studies have found increased serum levels of inflammatory biomarkers in depressed patients and decreased levels after antidepressant pharmacological intervention (Dowlati et al., 2010; Dunjic-Kostic et al., 2013; Himmerich et al., 2008; Lanquillon et al., 2000; Leonard, 2014). Other studies have associated non-pharmacological interventions (e.g. exercise, electroconvulsive therapy, sleep deprivation, relaxation) both with depressive symptoms and inflammatory markers (Branco et al., 2014; Buel et al., 2015; Carneiro et al., 2015; Irwin et al., 2015; Jr. et al., 2015; Kéri et al., 2014; Ranjbar et al., 2015). However, literature is yet to reveal if the reduction of depressive symptoms after psychotherapy is accompanied by a reduction in pro-inflammatory cytokines serum levels. One pilot study evaluated the changes in IL-6 levels after seven sessions of cognitive-behavioral psychotherapy and revealed a significant decrease in the IL-6 levels after the intervention (Gazal et al., 2013). Another study found a significant decrease in the severity of depressive symptoms and serum IL-6 and TNF—α after cognitive-behavioral psychotherapy, but not in narrative cognitive therapy (Moreira et al., 2015). Moreover, one study on cognitive therapy for depression and peripheral oxidative stress parameters found that cognitive psychotherapies were able to counteract peripheral oxidative stress in depressed patients, reducing thiobarbituric acid reactive species (TBARS) levels in the follow-up, nitric oxide in the post-treatment and follow-up, and increasing the total thiol content in the post-treatment and follow-up (Kaufmann et al., 2015).

In terms of psychotherapy, the key interventions for depression in primary care settings are treatment with generic antidepressant drugs and brief psychotherapy. Studies reveal a significant reduction of depressive symptoms after short-term psychodynamic psychotherapy at post-treatment and at follow-up (Bressi et al., 2010; Driessen et al., 2010; Leichsenring, 2001). It may strengthen the patient's abilities of realistic adaptation, insight, problem-solving, and rectification, through the elucidation of basic aspects of the patient's current situation (Fiorini, 2008). Moreover, there is a need for laboratorial measures to indicate treatment termination due to the limitation of self-report instruments.

Having considered this background, the aim of this study was to investigate the reduction of depressive symptoms and concomitant changes in pro-inflammatory cytokine levels in depressed patients before and after sixteen sessions of brief psychodynamic psychotherapy.

2. Methods

This was a quasi-experimental study that evaluated depressed patients who participated in a randomized clinical trial conducted in a mental health ambulatory (Pelotas/Brazil). The clinical trial tested the efficacy of two short-term psychotherapeutic models for depression (Supportive Expressive Dynamic Psychotherapy and Cognitive-Behavioral Psychotherapy). This work presents data from the dynamic psychotherapeutic model only. The clinical trial is nested within an outpatient research and mental health evaluation service from the Catholic University of Pelotas.

3. Recruitment

Public health facilities in the urban area of Pelotas, including primary care and mental health units, were contacted. Recruitment also included advertisements at local media and referral from other research works at the university.

4. Participants

This was a convenience sample. The participants were individuals who have voluntarily sought our psychology service (after reading or hearing about the research in the media) wishing to receive treatment; or had been referred from the public facilities where recruitment took place.

Every patient responded to a questionnaire about gender, age, schooling (years), socioeconomic status, current use of psychiatric medication, chronic clinical disorders (spinal problems, arthritis or rheumatism, cancer, diabetes, bronchitis or asthma, hypertension, cardiac problems, kidney insufficiency, tuberculosis, tendinitis or synovitis, cirrhosis, or other), current tobacco use/abuse, and current alcohol abuse. Major Depressive Disorder and comorbidities were evaluated by a Psychologist previously trained regarding evaluation methods and who attended to weekly supervision meetings. In case of any doubts concerning the diagnosis, patient was furtherly evaluated by a psychiatrist from the research team.

Patients who were diagnosed with MDD were included in the clinical trial if they had signed informed consent and if they fulfilled the following criteria: (1) MDD was the only or the most distressing current disorder; (2) the patient agreed to the treatment; (3) the patient was not currently using or had used any antidepressant medication in the two months prior to the treatment; (4) the patient did not present moderate or severe suicide risk; (5) there was no dependence of alcohol and/or abuse of illegal substances; (6) there were no psychotic symptoms. Thus, only patients with mild or moderate depression were included in the trial.

5. Data collection

Data collection occurred from July 2012 to June 2015. Blood samples were obtained at baseline and post-treatment (sessions 1 and 18) of psychotherapeutic treatment. Samples were obtained at a proper lab at the University, on the same Campus of the Psychological Clinic from the Catholic University of Pelotas, where psychotherapy sessions were carried out. Instruments on depressive symptoms were also administered at sessions 1 and 18.

6. Outcomes

The diagnosis of Depression and comorbidities was carried out using the Mini International Neuropsychiatric Interview (MINI)