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Role of pentoxifylline as an adjuvant therapy in treatment of adult patients with major depressive disorder

A proposal submitted for partial fulfillment of Doctor of Philisophy degree in Pharmacy (Clinical Pharmacy)

By

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Introduction

Major depressive disorder (MDD) is a common and sometimes fatal disorder that is a leading cause of disability worldwid [1]. Available antidepressant medications, which largely target monoamine and serotonin pathways, are effective; however, more than 30% of depressed patients fail to achieve remission despite multiple treatment trials [2].

Chronic inflammation has been implicated in the pathophysiology of MDD [3-5]. It has been established that pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) induce not only symptoms of sickness, but also true major depressive disorders in physically ill patients with no previous history of mental disorders [6, 7]. Changes regarding the immune system and specifically the cytokine system in which TNF-α is a pro-inflammatory key signalling molecule have been shown to be involved in the development of psychiatric disorders [8-10]. TNF-α might contribute to the pathogenesis of depression, it reduces the production of central serotonin (5-HT) neurotransmitter by stimulating the enzyme indoleamine 2,3-dioxygenase (IDO), which converts tryptophan, the precursor of 5-HT, into kynurenine. Overstimulation of IDO lead to depletion of tryptophan and, therefore, reduces synthesis of 5-HT in the brain [11, 12]. In addition, a growing body of evidence also points to increased oxidative stress in MDD. Elevated plasma level of oxidative stress markers were found in patients with MDD (e.g., increased 8-hydroxydeoxyguanosine [8-OHdG] or F2-isoprostanes [13].

Pentoxifylline (PTX), a methylxanthine-derivative and nonspecific phosphodiesterase inhibitor with combined anti-inflammatory and antifibrogenic properties [14], can lower the levels of circulating proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, by means of a cyclic adenosine monophosphate (cAMP)-dependent mechanism [15]. Furthermore, pentoxifylline has been proposed to have antioxidant properties [15]. Moreover, pentoxifylline facilitates synthesis and release of serotonin and inhibits its uptake, suggesting that pentoxifylline enhances serotonergic presynaptic response in the CNS [16]. In addition, it showed antidepressive-like effects in a rat model of acute myocardial infarction [17].

Aim of the study

The aim of the current study is to evaluate the potential antidepressant effect of pentoxifylline in adult patients with MDD. We hypothesized that MDD patients taking pentoxifylline as adjuvant would present greater amelioration of their depressive symptoms than patients taking placebo. Furthermore, we will assess the relationship between HAM-D score and several peripheral biomarkers as well as their role in diagnosis and therapeutic targets of MDD.

Patients and methods

Eighty adult outpatients who will meet the diagnostic and statistical manual of mental disorder IV (DSM-IV) criteria for major depression will be participated in the trial [(18)]. Patients will be recruited from the armed psychiatry hospital, Egypt. Patients have a baseline Hamilton Rating Scale for Depression (Ham-D) score of at least 18 [(19)]. Patients will be allocated in a random fashion: 40 patients will receive escitalopram 20 mg/day plus placebo (Control group) and 40 patients will receive escitalopram 20 mg/day plus pentoxifylline 800 mg/day (400mg bid) (morning and evening). Treatment duration will be 12 weeks. Adherence to the study medication will be assessed by collecting the empty blister packs of the consumed drugs from the patients every 4 weeks. Patients will be assessed by a psychiatrist at baseline, 4, 8, and 12 weeks after starting the medication. Any unexpected risks appeared during the course of the research will be cleared to participants and the ethical committee on time. An informed consent will be obtained from all participants in this research.

Measurements:

1. Full patient history, demographic data and clinical examination.
2. Patients will be assessed by a psychiatrist at baseline, 4, 8, and 12 weeks after starting the medication. The principal measure of the outcome will be the 17-item Ham-D. Remission is defined as an endpoint Ham-D total score < or = 7. Treatment response is defined as at least 50% improvement during the study period in the Ham-D scale. The mean decrease in Ham-D score from baseline will be the main outcome measure of response of depression to treatment (Primary outcome).
3. Questinnaire to evaluate the side effects of the study medications.
4. **Biological markers (Secondary outcome)**: Blood sample collection at baseline and after the treatment to evaluate the following:
   i) Serum level of Brain-derived Neurotrophic Factor (BDNF)
   ii) Serum Serotonin level
   iii) Serum levels of the following proinflammatory and anti-inflammatory markers:
      - Tumor necrosis factor-alpha (TNF-a)

- Interlukin-6 (IL-6)
- Interlukin-10 (IL-10)

iv) Serum levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of oxidative damage.

Inclusion criteria:

1- Eighty adult outpatients with the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of MDD based on a MINI Neuropsychiatric Interview (MINI) (American Psychiatric Association., 2000; Sheehan et al., 1998), without psychotic features and a total 17 item HAM-D score of at least 18 with item 1 (depressed mood) scored 2 or greater were eligible.

2- Patients were requested to be free of all the psychotropic and anti-inflammatory medications for at least 4 weeks before participating in the study.

Exclusion criteria:

1. Patients with bipolar I or bipolar II disorder
2. Patients with personality disorders
3. Patients with eating disorders
4. Patients with substance dependence or abuse
5. Patients with concurrent active medical condition
6. Patients with history of seizures
7. Patients with history of receiving Electroconvulsive therapy (ECT)
8. Patients with inflammatory disorders
9. Patients with allergy or contraindications to the used medications
10. Patients with finally pregnant or lactating females

Statistical analysis:

All tests of treatment effect will be conducted by external statistician blind to group allocation, at a two-sided significance level of 0.05, and no adjustments were made for multiple comparisons. Type III sums of squares will be used to adjust for unbalanced data in the interactions of these models of variance. Importantly, general linear model for analysis of covariance (ANCOVA) model will be used for the primary analysis of change from baseline to endpoint in HAM-D total score. The primary analysis was performed using a mixed-effects model repeated measures (MMRM) ANCOVA. As a sensitivity analysis, will be carried out using the last observation carried forward (LOCF) approach in case of dropouts. Furthermore, a two-way repeated measures analysis of variance (ANOVA) for HAM-D score (time–treatment interaction) will be used. The two groups as a between-subjects factor (group) and the four time interval measurements during treatment as the within-subjects factor (time) will be

considered. Moreover, repeated measures ANOVA will be used to test the time x group interaction on the changes in the biomarkers between baseline and week 12 in the two groups. Chi square test was used for the qualitative variables. The statistical analysis was performed with IBM©SPSS® Statistics V 22. Pearson's correlation will be calculated to assess the relationship among variables.

References:

1- **Moussavi S, Chatterji S, Verdes E, et al**. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007; 370(9590): 851-8.

2- **Miller AH, Maletic V, and Raison CL**. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological Psychiatry. 2009; 65(9):732-41.

3- **Berk M, Kapczinski F, Andreazza AC, et al**. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neuroscience & Biobehavioral Reviews. 2011; 35(3): 804–17.

4- **Capuron L and Miller AH**. Immune system to brain signaling: neuropsychopharmacological implications.Pharmacology & Therapeutics. 2011; 130(2):226-38.

5- **Himmerich H, Fulda S, Linseisen J, et al**. Depression, comorbidities and the TNF-alpha system. European Psychiatry. 2008; 23(6):421-9.

6- **Krügel U, Fischer J, Radicke S, et al**. Antidepressant effects of TNF-α blockade in an animal model of depression. Journal of Psychiatric Research. 2013; 47(5):611-6.

7- **Slavich GM and Irwin MR**. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychological bulletin. 2014; 140(3):774-815.

8- **Himmerich H, Berthold-Losleben M, and Pollmächer T**. The relevance of the TNF-alpha system in psychiatric disorders. Fortschritte der Neurologie - Psychiatrie. 2009; 77(6):334-45.

9- **Himmerich H, Fulda S, Linseisen J, et al**. Depression, comorbidities and the TNF-alpha system. European Psychiatry. 2008; 23(6):421-9.

10- **Schmidt FM, Kirkby KC, and Himmerich H**. The TNF-alpha inhibitor etanercept as monotherapy in treatment-resistant depression - report of two cases. Psychiatria Danubina. 2014; 26(3):288-90.

11- **Reichenberg A, Kraus T, Haack M, et al**. Endotoxin-induced changes in food consumption in healthy volunteers are associated with TNF-alpha and IL-6 secretion. Psychoneuroendocrinology. 2002; 27(8):945-56.

12- **Köhler O, Benros ME, Nordentoft M, et al**. Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Journal of the American Medical Association psychiatry. 2014; 71(12):1381-91.

13- **Rawdin BJ, Mellon SH, Dhabhar FS, et al**. Dysregulated relationship of inflammation and oxidative stress in major depression. Brain, behavior, and immunity. 2013; 31:143-52.

14- **Gutierrez-Reyes G, Lopez-Ortal P, Sixtos S, et al**. Effect of pentoxifylline on levels of pro-inflammatory cytokines during chronic hepatitis C. Scandinavian Journal of Immunology. 2006; 63(6):461-7.

15- **Akhondzadeh S, Fallah J, Mohammadi MR, et al**. Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2010; 34(1):32-6.

16- **Gupta S**. Immunological treatments for autism. Journal of Autism and Developmental Disorders. 2000; 30:475–9.

17- **Bah TM, Kaloustian S, Rousseau G, and Godbout R**. Pretreatment with pentoxifylline has antidepressant-like effects in a rat model of acute myocardial infarction. Behavioural Pharmacology. 2011; 22(8):779-84.

18- **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., Text Revision. Washington, DC: American Psychiatric Association; 2000.

19- **Hamilton M**. A rating scale for depression. Journal of Neurology, Neurosurgery & Psychiatry.1960; 23:56-62.