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Effect of Celecoxib in addition to standard therapy in adults with Major Depressive Disorder: A double-blind, randomized clinical trial

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ABSTRACT

Introduction: Major depressive disorder (MDD) is an important cause of disability and only about 50% of patients achieve remission with standard antidepressant treatment. There is evidence that inflammatory mechanisms mediate the development and progression of this disease. However, controversy remains about the use of anti-inflammatory drugs as a therapeutic option for MDD. **Research Hypothesis:** Patients with MDD who receive celecoxib plus standard therapy achieve a lower score in the Hamilton rating scale for depression (HRSD) when compared to placebo plus standard therapy. **Methods:** A total of 80 out-patients from the Mental Health Service of the Fundacion Santa Fe de Bogotá, aged 20-40 years old, with a diagnosis of moderate or severe MDD without previous treatment in the last 6 months will be included. Patients will be randomized to Celecoxib or placebo with an allocation ratio of 1:1 using a web-based random number generator. The primary endpoint will be the difference between the pretest and posttest score of the HRSD, after 6 months of treatment. **Feasibility:** This trial is feasible and relevant to the theme, in spite of the difficulty to maintain adherence in a study with MDD. **Anticipated Results:** Decrease in HRSD is expected in both groups during follow-up, but it is expected to be larger in the celecoxib group. A more rapid decrease of HRSD scores is expected in the 1st weeks.

KEY WORDS: Celecoxib, depression, treatment

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INTRODUCTION

Depression is a common mental disorder, characterized by sadness, loss of interest, feelings of low self-worth, tiredness, and poor concentration, that impairs a person's ability and at its most severe can lead to suicide (WHO, 2014). It is one of the leading causes of disability worldwide, with major depressive disorder (MDD) having a lifetime prevalence of approximately 12-15% [1]. In Colombia, larger and more recent population studies are lacking, however a cross-sectional study showed a prevalence of MDD of 11.2% [2]. Despite the substantial drug development over the last decades, remission is still not achieved in approximately 40-50% of patients [3,4], so new therapeutic strategies are necessary to improve disease management.

Over the last 20 years, novel experiments in MDD pathogenesis have suggested that inflammatory mechanisms play an important role in disease development and progression [5]. Important mediators of inflammation such as prostaglandin E2 (PGE2) and IL6 are found increased in patients with depression. Cyclooxygenases (COX) are the enzymes involved in PG synthesis, of which COX-2 is cytokine-inducible, expressed in inflammatory cells and is also responsible for PGs produced in inflammation [16]. Two double-blind, randomized, placebo controlled, add-on, pilot studies investigated the efficacy of celecoxib, a COX-2 inhibitor, as an adjunct in the treatment of depression, i.e., reboxetine [15] and fluoxetine [16]. Both studies concluded that celecoxib may be an effective add-on treatment of clinical depression, although these effects need further validation by studies with a sufficient sample size.

We propose to run a larger randomized, placebo-controlled trial in patients with MDD from Colombia, in order to validate the therapeutic effects of celecoxib as an adjunct to standard therapy.

Research Hypothesis

Adults (20-40 years old) with MDD who receive celecoxib plus standard therapy (fluoxetine and cognitive behavioral therapy [CBT]) in comparison to those who receive placebo plus standard therapy will have a significant greater reduction in the score of the Hamilton Rating Scale for Depression (HRSD) after a period of 6 months.

METHODS

Study Design

This is a prospective double-blind, randomized, placebo controlled clinical trial of parallel groups of patients with MDD, studying celecoxib as an add-on to standard therapy (fluoxetine and CBT).

Study Population

Participants will be recruited at the outpatient's Mental Health Service of the Fundacion Santa Fe de Bogotá, Colombia, by certified psychiatrists. Patients will be diagnosed with MDD, according to the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) of Mental Disorders [6], by using the Structured Clinical Interview for the DSM-IV Axis I Disorders [7]. Severity of depression will be assessed by the physician with the HRDS [8] and the Beck Depression Inventory (BDI) [9].

Patients will be invited to participate of our study if they meet the inclusion criteria: Adult out-patients between 20 and 40 years-old; clinical diagnosis of nonpsychotic and nonbipolar major depression; have never been treated or have been at least 6 months without antidepressive treatment; and at least moderate depression, measured as >13 in the HRSD score.

Patients will be excluded if they have diagnosis of any organic brain syndrome, psychotic or bipolar disorder, schizophrenia, obsessive-compulsive disorder, panic syndrome, anorexia, or bulimia. Patients will also be excluded if they have current or history within the past 6 months of any drug abuse or dependence including alcohol. Patients should not have used any anti-inflammatory within the 4 weeks prior to enrollment. Participants will not be enrolled if they have known allergy to celecoxib, fluoxetine, or are in use of any drugs that have potential interaction with medications used in the trial. Specific criteria to women include not being pregnant, or lactating, and for those who are in the fertile period, they should be using a contraception method. Patients who have any unstable or severe medical condition that requires hospitalization, or have high cardiovascular disease risk (blood pressure above 140/90 mmHg, dyslipidemia, diabetes, history of coronary artery disease, stroke, and claudication) will be excluded. Laboratory screening will be performed and patients will be excluded if they present results outside reference ranges, defined as: Hemoglobin levels of 13.5-17.5 g/dL for males and 12-16 g/dL for females; aspartate transaminase levels ≥ 40 IU/L; alanine transaminase levels of ≥ 50 IU/L; creatinine clearance of 90-136 mL/min/1.73 m^2 for males and of 80-125 mL/min/1.73 m^2 for females; thyroid stimulating hormone of 0.5-4.7 μIU/mL and T4 free of 0.8-2.3 ng/dL. Special attention will be given for renal function because of non-steroidal anti-inflammatory use in the trial.

Participants Recruitment

We will use target enrollment strategies by contacting psychiatrists in the study center, using letters and e-mails to tell them about our study and ask them to refer their patients. We will also use public awareness campaigns, through posters in public hospitals and brochures distributed in public places of Bogota. The recruitment period will be of 2 years or until the number patients reach the calculated sample size.

Randomization

After signing the informed consent and documenting the eligibility based on the inclusion and exclusion criteria, eligible patients will be randomly assigned to celecoxib or placebo with a treatment allocation ratio of 1:1 using the web-based random number generator Intergers [19]. We will use permuted blocking

(with first block size = 4, and subsequent random block sizes of 4 and 6) to avoid imbalance between groups, in order to ensure the qualitative equality between groups regarding covariates. Clinicians will receive the number for the subject and the kit containing either the celecoxib or placebo. Patients will be considered randomized as soon as the first allocation of treatment kit number is documented by the clinician.

Intervention

The subjects will be divided into two groups: (1) Patients will receive fluoxetine (40 mg/day) plus CBT plus oral celecoxib (400 mg/day) (200 mg bid, morning and evening); or (2) Patients will receive fluoxetine (40 mg/day) plus CBT plus oral placebo (1 capsule bid, morning and evening) [Figure 1].

The capsules will be white with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body. They will be for oral administration and contain either 200 mg of active celecoxib or matching placebo. They will also contain excipients including croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, and sodium lauryl sulfate.

The patients will orally take 2 capsules of celecoxib or matching placebo, daily during 24 weeks without regard to time of meals.

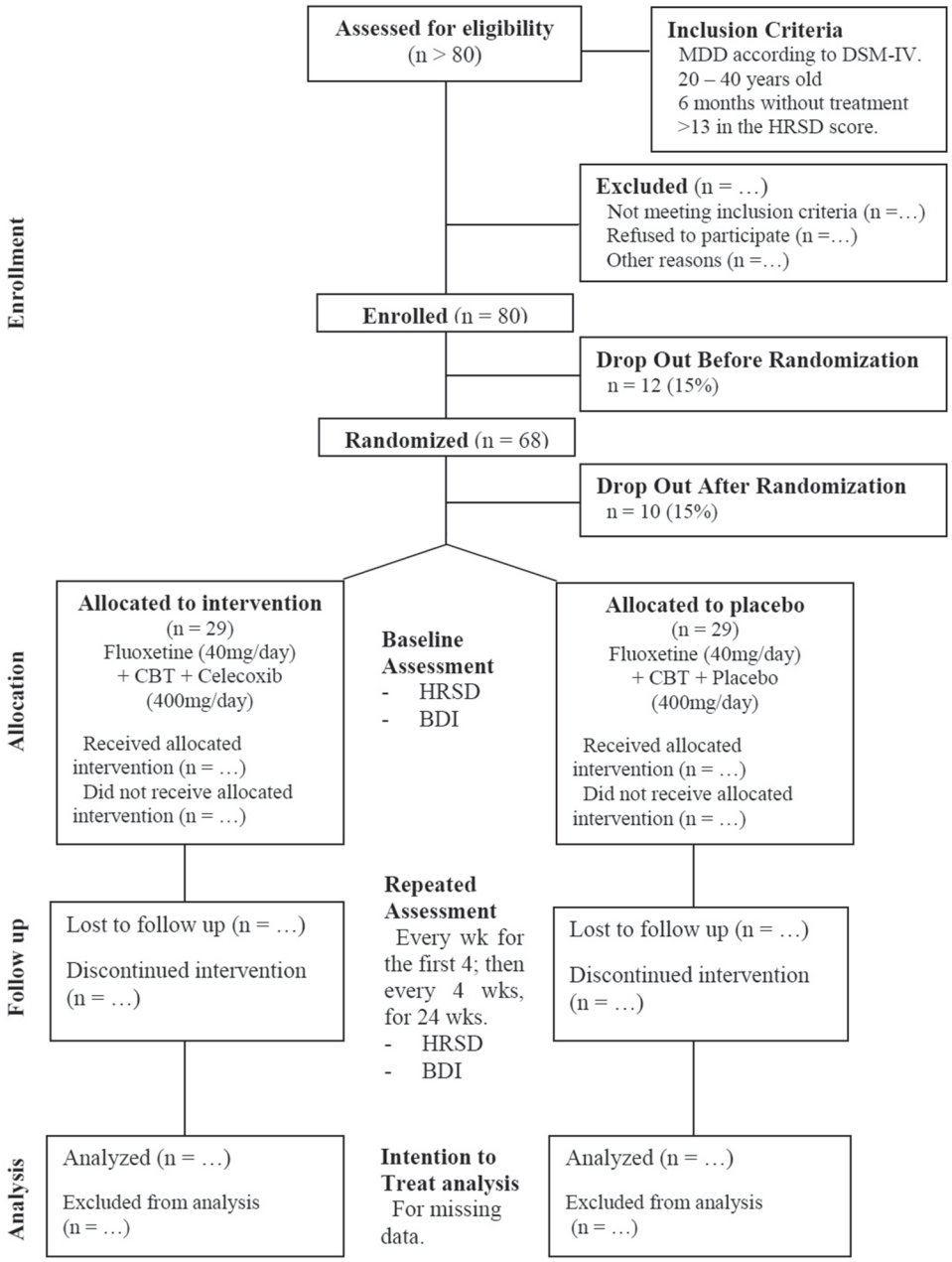

Figure 1: Study design flowchart, Note: MDD: Major depressive disorder, HRSD: Hamilton rating scale for depression, BDI: Beck Depression Inventory, CBT: Cognitive behavioral therapy, wk: week

Furthermore, a capsule of fluoxetine 20 mg will be given for the first 2 weeks, after which the dose will be increased to fluoxetine 40 mg per day for the rest of the trial. The celecoxib or placebo and the fluoxetine, will be refilled with enough treatment for the patient every 2 or 4 weeks. Besides, participants will meet with their therapist on a weekly basis. CBT will be based on the manuals of Beck [10,11]. Sessions will last for 60 min and will be recorded to supervise treatment integrity. Only the authors of the study will have access to these records. Therapists in the study will be psychiatrists or clinical psychologists with at least 2 years of experience in CBT. Therapy integrity will be monitored during training and study phases.

Blinding

This will be a double-blinded study; both patients and data collectors (therapists) will be blinded to treatment allocation of intervention or placebo. Owing to its subjective outcomes (HRSD and BDI scale), the double-blinding is extremely important in order to make results more reliable. We will assess blinding by asking patients and data collectors to guess in which group each patient has been allocated to at the beginning and at the end of the study.

Assessments

The HRSD is a clinician-rated scale designed to assess depression severity among patients. The 17-item version of the HRSD will be used, which has become the standard for clinical trials and is on average applied in 20 min. Scores between 0 and 7 indicate absence of depression; scores 8-13 indicate mild depression; 14-18 indicate moderate depression; 19-22 indicate severe depression and scores ≥ 23 indicate very severe depression [8].

The BDI II is a 21 question self-report inventory and is one of the most widely used instruments for measuring the severity of depression. A score of 0-13 in this scale indicates minimal depression; a score of 14-19 indicates mild depression; a score of 20-28 indicates moderate depression, and a score of 29-63 indicates severe depression [9].

At enrollment, patients will take the HRSD and the BDI, as a baseline. Afterwards, patients will keep a journal and continue with a therapist every week for the CBT. Patients will retake both tests every week for the first 4 weeks and then every 4 weeks until 24 weeks of treatment have been completed. If during the study, any patient couldn't be followed or data is missed, the last score recorded from the patient will be considered (last observation carried forward).

Adherence

Adherence will be assured by using effective communication and reminders, enhancing of patient-provider relationship with clear explanations of expected symptoms, and closed follow up by checking the number of pills taken by each patient when they come to receive their medication for the next period. When patients with poor adherence is identified, we will try to enhance adherence by using the following strategies: Addressing possible barriers to take the medication identified by the patients, involve family members when feasible, and repeatedly provide simple and clear instructions on how to take the medications. Adherence will be stimulated by weekly phone calls or appointments; patients will pick pill box every month filling a container that can keep track when the pills are being emptied; and if they do not come for an appointment they can reschedule it within 4 days maximum.

Endpoints

The primary endpoint will be the difference between the pretest and posttest score of the HRSD, after 6 months of treatment.

Secondary outcomes will include the difference in the pretest and posttest score for the BDI-II after 6 months of treatment. We will also analyze the change in the score every 4 weeks compared with the initial score, with both scales.

Sample Size Calculation

The first challenge here is to determine the clinically meaningful changes in the HRSD scale. In the paper by Raison *et al.* [12], which studies infliximab versus placebo in addition to standard therapy in MDD non-responders to antidepressants, the placebo group experienced a mean reduction of approximately 10 points in HRSD scale over 12 weeks, but the infliximab group was not statistically different. In the paper by Sepanjnia *et al.* [13], which compared pioglitazone versus placebo in addition to citalopram over 6 weeks in patients with MDD, showed a mean difference between groups in HRSD change from baseline of −3.4 (−5.6, −1.2) with $P = 0.005$. However, the mechanism of action was different.

When interpreting HRSD scale in a clinical setting, one has to look at the 5 categories: Normal (0-7), mild (8-13), moderate (14-18), severe (19-22), and very severe (23-38). The minimum distance between the middle points of the categories is 4.5 (between moderate and severe). If we assume that the treatment group would have a clinically meaningful effect, we have to assume that the treatment group will have a mean change in HRSD scale greater than placebo group of 4.5 points or more. This study reported confidence intervals that allowed the calculation of the common variance of the mean difference. The variance was equal to 5. In the article by Furukawa *et al.* [14], the authors define improvement in HRSD as follows: Very much improved = reduction of 18+ points; much improved = reduction of 11-17 points; minimally improved = reduction of 4-10 points; other changes = no change. Based on this paper we will use an effect size of 4 points on the HRSD between groups for sample size calculation. In summary, the minimal clinically significant difference between the groups will lie between 4 and 4.5 points, with a common variance of 5.

Since we aimed to compare the mean difference from baseline to the end of the trial, we used an unpaired t-test to calculate the sample size. Assuming alpha = 0.05, power = 0.80,

1:1 case: control ratio, detectable difference of at least 4 points, variance = 5, the minimum needed number per group is 26 patients.

Only one previous study showed approximately 17% of drop out before randomization, whereas in three studies 0% - 15% of drop out was encountered after randomization [13,16,18]. Staying conservative and considering a total drop out percentage of 32%, the total sample size required for this study will be 80 patients.

Statistical Analysis

Patients will be evaluated at baseline, then for every week for the first 4 weeks and afterwards every 4 weeks for the total of the 24- week study period. The primary endpoint, the difference between the pretest and posttest score of the HRSD, from baseline to 6 months, will be analyzed with unpaired t-test. The secondary endpoints will be analyzed with two-way repeated measures analysis of variance ANOVA (time-treatment interaction). To minimize type I error, Bonferoni's correction will be used as a post hoc test. If data is not normally distributed, Mann-Whitney test will be used. Intention to treat analysis with last observation carried forward procedure will be performed to deal with missing data. For all analysis, differences will be considered significant with $P \leq 0.05$.

To assess if there are significant differences in the baseline characteristics (e.g., demographic data) between the randomized groups, Chi-square test or unpaired t-tests will be performed for categorical and continuous data respectively.

Feasibility and Ethical Concerns

This study is very relevant due to the high prevalence and burden of depression and the need of new effective treatments. We have designed a study which tries to resemble the clinical setting, but controlling some covariates to reduce confounding. However, this study has some potential limitations. The first pitfall is the difficulty of working with patients with a psychiatric disorder. Recruitment and adherence to the treatment as well as follow-up of the patients may be a problem. To deal with this limitation, we added a high dropout rate (32%) to our sample size calculation.

In past studies few problems were encountered to enroll patients [13,16,18]. Probably the main one will be the concern for privacy of information and adverse effects. To address these problems, the management of data and health surveillance will be explained to the patients. All participants should sign a written informed consent prior to enrollment into the clinical trial.

Other possible potential limitations are the adverse effects that patients may have with medications used in this trial. Selective serotonin reuptake inhibitors (SSRIs) increase the risk of gastrointestinal hemorrhage, whereas COX-2 inhibitors increase the risk of thrombotic events. In every medical appointment, the general physician will actively look for any symptoms involving these adverse effects; also patients will keep a diary where they can write side-effects and suicidal thoughts. Besides helping physicians to assess depression severity, this diary will point out the presence of side-effects, in which case, the patient will be treated and withdrawn from the trial.

Since this project will be dealing with patients, an IRB and Ethics Committee approval will be necessary before starting this study.

Anticipated Results

There are few publications on efficacy of COX-2 inhibitors in depressed patients. According to these publications, a statistically significant decrease in HRSD scores should be expected in both groups, but it can be greater under celecoxib treatment conditions. Müller *et al.* [15] found that HRSD scores decrease in 55% in the reboxetine + celecoxib group, and 33% in the reboxetine + placebo group. The difference between groups after 6 weeks of treatment was about 8. The results of another study [16] showed a difference of 3 points of HRSD. Therefore, we can expect similar results in terms of HRSD scores changing.

During the 6 months of the study, it is expected that the decrease of the HRSD scores will not be linear. Curves reflecting changing of HRSD scores may rapidly decrease during the first 4 weeks of the trial. After that, changing of depressive symptoms may be smaller. Both groups may have similar curves, but placebo group is expected to have less prominent changes. It is possible that depression symptoms may be increased at the beginning of the study, especially in the placebo group.

We do not expect to find a large effect size due to the design of this study. There will be comparison between 2 groups, each of them will receive two treatments (pharmacological therapy and psychotherapy); therefore, additional effect of celecoxib can be masked by basic antidepressive treatment.

Secondary endpoint is the score in the BDI II. There is data confirming HRSD and BDI-II scores are positively correlated [9]. Accordingly, we can expect unidirectional changes of these scores.

Safety data in the results of Akhondzadeh [16] and Müller [15] studies were identical for placebo and celecoxib groups. We expect that therapy with 400 mg/day of celecoxib will be well-tolerated with no clinically important side effects as suggested by Akhondzadeh *et al.*, despite the longer period of intake [16].

DISCUSSION

MDD is one of the leading causes of disability worldwide: One in four people experience it during their lives [16]. Despite substantial progression in drug development, about 50% of these patients do not achieve complete remission [3,4]. Even with successful treatment and following remission, quality of life is still threatened by residual symptoms (such as social and cognitive impairment) and by the risk of relapse [17]. Since the benefit of the currently used therapy is not always clinically

significant [3], more therapeutic options are needed to target this condition.

In a randomized double-blind trial, 40 patients suffering from an acute depressive episode were assigned to take reboxetine associated with either celecoxib or placebo during 6 weeks. Although both groups presented improvement in HRSD, the group that received celecoxib adjuvant therapy had significantly greater improvement compared with the placebo group [15]. These data suggest that celecoxib would have significant positive effects on the depression treatment in patients with depressive symptomatology in the group that will receive celecoxib with fluoxetine in our research. Similar results were reported in a more recent study from Akhondzadeh *et al*., in which the intervention group (fluoxetine plus celecoxib) was superior to fluoxetine-placebo group in reducing HRSD scores after 6 weeks. Furthermore, a study of bipolar patients with depressive episodes has reported that celecoxib produced a rapid-onset antidepressant effect as compared to placebo in a period of 6 weeks [18]. In line with our research hypothesis, the celecoxib group should have significantly greater improvement over a period of 6 months in comparison with placebo group with standard treatment. Therefore, the results of this study may support the enhancement of the antidepressant effect of the SSRI fluoxetine by concurrent treatment with celecoxib in a longer period of intervention, thus providing evidence for its clinical employment in MDD treatment.

On the other hand, there are negative reports on the clinical efficacy of COX-2 inhibitors [20]. The results of a cross-sectional study showed associations of inflammatory markers with age, smoking, alcohol use, body mass index, physical activity, somatic disease, and medication [21]. Due to heterogeneity of depressive disorders, we can suppose there are certain subgroups of patients, which can benefits from COX-2 inhibitors. For this reason, the mechanism through which anti-inflammatory therapies can affect depressed should be further investigated.

The pathogenesis of MDD, as well as the antidepressant effects of COX-2 inhibitors, is still not completely understood [5]. The cytokine hypothesis has been consistently proven by the enhanced pro-inflammatory mediators (such as interleukins 1, 2, 6 and 8, and tumor necrosis factor-α) in MDD patients [22]. Therefore, COX2 inhibitors suppression of PGs synthesis (specifically PGE2), which are stimulated by those cytokines, could explain the therapeutic role of anti-inflammatory drugs. Moreover, they seem to act on serotonergic system through immune mechanisms and on noradrenaline neurotransmission by inhibiting PGE-2-mediated reduction of noradrenaline release by central neurons [23]. This strengthens the potential of measuring cytokines in patients as a predictor of treatment response [5]. The main concern of this study is the clinical response in depression symptoms, therefore, although anti-inflammatories are being used, we will not measure inflammatory parameters.

There are some limitations to this study; HRSD is a standardized test in research to measure improvement in depression. Bias may arise when using a subjective scale (e.g., Hawthorne effect or experimenter expectancy). To avoid this problem, we have designed a double blinded study with a control group. On the other hand, Akhondzadeh *et al*. reported the difficulty of controlling if the patients took other medications due to out-patient setting of research [15]. Although we addressed this issue in study design, it can still be a limitation to our trial. Other recent study results reported an increased risk for cardiovascular problems due to celecoxib intake [20]. Moreover, as with all NSAIDs, there is a potential risk of gastric bleeding when taking celecoxib. Although this is a rare side-effect with celecoxib, it is still an alarming possibility, especially with prolonged use [15]. This study distinguishes from previous ones done in the methodology used. These results should elucidate if there is a real benefit in using commonly used anti-inflammatories such as Cox-2 inhibitors, in adjunct treatment for MDD, by improving response of standard antidepressants when used for longer period of treatment.

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