Celecoxib added to mood stabilizer for treating acute mania in bipolar disorder: A randomized, double-blind, placebo-controlled trial in IRAN

Farhad Faridhosseini
Mashhad University of Medical Sciences

Ali Talaei
Mashhad University of Medical Sciences

Najmeh Shahini (✉ najmeh.shahini@gmail.com)
goelstan research cener of psychiatry , goelstan university of medical sciences,gorgan ,iran
https://orcid.org/0000-0001-7781-6014

Mahbobeh Eslamzadeh
Mashhad University of Medical Sciences

Samira Ahrari
Texas A&M University System Health Science Center College of Medicine: Texas A&M University College of Medicine

Meysam Poorgholami
Shahid Beheshti University of Medical Sciences: Shaheed Beheshti University of Medical Sciences

Mohammadzaman Kamkar
Golestan University of Medical Sciences and Health Services

Majid Khadem Rezaeian
Mashhad University of Medical Sciences

Research

Keywords: Celecoxib, Clinical trial, acute mania

DOI: https://doi.org/10.21203/rs.3.rs-237985/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Background:** Inflammatory processes in the brain contribute to the aetiopathogenesis of acute mania. Cyclooxygenase-2 (COX-2) inhibitors, such as Celecoxib, reduce the production of pro-inflammatory cytokines. The purpose of the present investigation was to assess the efficacy of Celecoxib in the treatment of acute mania.

**Methods:** We conducted a double-blind, placebo-controlled trial at the Specialty in-patient Clinic of Ibn-e-Sina Hospital [Mashhad University of Medical Sciences, Iran] from March 2017 to August 2017. The study involved 58 patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for acute mania screening to participate in the trial were used for the study. Twenty-three patients were assigned to a study group and were given Valproate Sodium 200 mg /BD plus Celecoxib 400 mg/day (200 mg BID). The control group included 22 patients who were given Valproate Sodium 200 mg /BD plus placebo. Patients were assessed by Young Mania Rating Scale (YMRS) at baseline 0, after 9, 18, and 28 days after the medication started. Data were analyzed by using Statistical Package for Social Sciences (SPSS) 11.5., two-way repeated measures analysis of variance, Fisher's exact test, and T-Test. $P \leq 0.05$ was considered to be statistically significant.

**Results:** A total of 58 patients were screened and 45 were randomized. Most of participations in celecoxib group were male (55%) and in placebo group were female (75%). There were no statistically significant differences between the groups regarding number of episode, sex, marital status, past medical history, past psychiatry history and family history $P$ value $\geq 0.05$. A significant difference was observed in the change of scores on Young Mania Rating Scale (YMRS) at week 4 as compared to the baseline in patient groups $P: 0.04$.

**Conclusion:** This study suggested that Celecoxib can be an effective adjuvant agent in managing patients with acute mania and anti-inflammatory therapies should further be investigated in these patients.

**Trial registration:** Iran clinical trial register: IRCT20200306046708N1

**Background**

In recent years, an increasing volume of evidence has shown the role of the inflammatory processes in the pathophysiology of psychiatric disorders, including schizophrenia, depression, and bipolar disorder (1–5). Bipolar disorder, characterized by recurrent episodes of mania, mixed and depression, is the most common major psychiatric disorder that is reported to have a prevalence of 0.5–4.3% in a recent systematic review of patients referred to the first level of care(6) and this prevalence could be higher in secondary and tertiary care levels. Also, according to the recent investigation of World Health Organization in eleven countries, the prevalence of bipolar disorder have been reported 2.4%(6, 7). As noted, many hypotheses have been proposed about the immunologic-inflammatory processes as part of the pathophysiology of bipolar disorder, as well as different mechanisms of action based on the
pathophysiology of mood stabilizers (8, 9), and it has recently been proposed that it may be better to view bipolar disorder as a multi-system inflammatory disease (10). Regarding manic episodes; also various evidences have shown the activation of the inflammatory process. For instance, in two recent studies, inflammatory immune system was significantly more active in patients with mania than the control group (11, 12), and one of these studies, an increase in the immune activity was a predictor of re-hospitalization of patients (12). A recent meta-analysis in bipolar disorder provided evidence of increased pro-inflammatory, anti-inflammatory and regulatory cytokines (13). Blood level of IL-6 in acute phase of mania was higher than the control group, and compared to the period of remission of symptoms and manic patients with high levels of interferon-gamma was associated with more severe clinical symptoms (based on the Yang mania scale) (14). It is also known that mood stabilizers such as lithium, sodium valproate, and carbamazepine down-regulate the inflammatory pathways in rat brain, and this effect may contribute to their efficacy in bipolar disorder (15–17). The therapeutic effects of IL-6 receptor antagonists have been also proposed in bipolar disorders (18). Celecoxib is an anti-inflammatory medication, and selective cox-2 inhibitor. Considering the role of cox-2 enzyme in the synthesis of prostaglandin E2 and that the prostaglandin stimulates biosynthesis of pro-inflammatory cytokines such as IL-6 (19), Celecoxib stop this process by inhibiting cox-2 enzyme. Despite an increase in the number and variety of medications, many patients in the acute phase of mania does not respond sufficiently (20, 21). Thus, combined treatment strategies of mood stabilizers with augmentation of atypical antipsychotics in the treatment of acute mania are commonly used. But regarding the widespread side effects of mood stabilizers (22), and the considerable prevalence of metabolic syndrome among bipolar patients (23), and concerning the role of the inflammatory processes in this disorder, the anti-inflammatory medication “Celecoxib” with a favorable profile of side effects without gastrointestinal adverse effects of other NSAIDs (24, 25) can be added as a potentially effective and safe option to the treatment of acute mania. Also all this may suggest that it is not about efficacy but effectiveness since it is a cohort of rats and not individuals. Therefore, in this study, we intended to evaluate the effectiveness of Celecoxib as adjunctive therapy in treatment of acute mania.

Methods/design

This study is a 4-week, randomized double blind, placebo-controlled clinical trial launched at the specialty in-patient clinic of Ibn-e-Sina Hospital [Mashhad University of Medical Sciences, Iran] from March 2017 to August 2017.

Participants

Fifty-four patients were considered for participation in the project if they met Diagnostic and Statistical Manual of Mental Disorders (DSM V) criteria for diagnosis of acute mania (26). A psychiatrist confirmed the diagnosis based on structured interview and a minimum score of 20 or above on the Young Mania Rating Scale (YMRS). The patients did not receive any psychotropic medications, such as selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), or monoamine oxide inhibitors
for 4 weeks preceding entry into the trial. Patients were excluded from the study if they have suffered from known autoimmune disease and were diagnosed with infectious diseases for at least 4 weeks prior to the beginning of the study. Also, patients were excluded if they met the criteria for major depressive disorder, eating disorders, personality disorders, mental retardation, a mental disorder due to general medical condition, substance dependence or abuse in the previous three months, history of seizures that would contraindicate the use of the medication of this study and receiving Electro-Convulsive Therapy (ECT) and peptic ulcers or a history of gastrointestinal bleeding, and use of any medications identified as contra-indicated with COX-2 inhibitors. Patients were prohibited from initiating psychotherapy after entry into the study. Pregnant women or women not using medically accepted means of birth control were excluded. Patients were required to be free of all psychotropic medications for at least 4 weeks before the study entry.

The protocol was approved by the IRB of Mashhad University of Medical Sciences. The patients and their legally authorized representative provided informed consent in accordance with the procedures outlined by the local IRB and were informed that they could withdraw from the trial at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (27). The trial was registered in Iran: IRCT20200306046708N1

**Interventions**

This study is a 4-week, randomized double blind, placebo-controlled clinical trial launched at the specialty in-patient clinic of Ibn-e-Sina Hospital [Mashhad University of Medical Sciences, Iran] from March 2017 to August 2017.

**Participants:**

Fifty-four patients were considered for participation in the project if they met Diagnostic and Statistical Manual of Mental Disorders (DSM V) criteria for diagnosis of acute mania (26). A psychiatrist confirmed the diagnosis based on structured interview and a minimum score of 20 or above on the Young Mania Rating Scale (YMRS). The patients did not receive any psychotropic medications, such as selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), or monoamine oxide inhibitors for 4 weeks preceding entry into the trial. Patients were excluded from the study if they have suffered from known autoimmune disease and were diagnosed with infectious diseases for at least 4 weeks prior to the beginning of the study. Also, patients were excluded if they met the criteria for major depressive disorder, eating disorders, personality disorders, mental retardation, a mental disorder due to general medical condition, substance dependence or abuse in the previous three months, history of seizures that would contraindicate the use of the medication of this study and receiving Electro-Convulsive Therapy (ECT) and peptic ulcers or a history of gastrointestinal bleeding, and use of any medications identified as contra-indicated with COX-2 inhibitors. Patients were prohibited from initiating psychotherapy after entry into the study. Pregnant women or women not using medically accepted means of birth control were
excluded. Patients were required to be free of all psychotropic medications for at least 4 weeks before the study entry.

The protocol was approved by the IRB of Mashhad University of Medical Sciences. The patients and their legally authorized representative provided informed consent in accordance with the procedures outlined by the local IRB and were informed that they could withdraw from the trial at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (27). The trial was registered in Iran: IRCT20200306046708N1

**Interventions:**

The investigator was provided with a sealed randomization code for each available medication number. Blinding was to be broken only if the patient’s trial medication would affect specific emergency treatment. Patients were randomized to receive Celecoxib (celebrex, Pfizer, 200mg capsule) or placebo in a 1:1 ratio using a computer-generated code. Patients were randomly given treatment for mania plus Celecoxib 400 mg/day (200 mg bid) (morning and evening) and treatment plus placebo for a 4-week, double-blind (participants, care providers, those assessing outcomes), placebo-controlled study. Five patients dropped out over the trial. Three patients from the Celecoxib group left the trial due to personal reasons unknown to the authors. One of the patients in the placebo group withdrew from the study due to vomiting and another patient discontinued the trial, because of early discharge

**Outcome:**

Patients were assessed with the YMRS at baseline (0), and 9, 18, and 28 day after the start of the treatment (3). A trained psychiatrist evaluated the patients during the treatment period using YMRS. The main outcome measure of this study was evaluation of celecoxib efficacy in improvement of YMRS total score compared to placebo. Partial response and complete response were defined as 25% and 35% reduction in the YMRS score, respectively.

**Safety outcomes:**

Side effects were systematically recorded through the study and were assessed using a checklist administered by a resident psychiatrist at baseline and 9, 18, and 28 days after the start of treatment.

**Sample size:** The sample was calculated according to the arccosine formula considering a power of 80% and a type I error of 0.05. Assigning a successful rate of 30% in the control group and 60% in the active group, 40 participants will be needed. After adjusting for a loss rate of 5%, the total number of patients that must be recruited is 50 (25 patients per group).

**Randomization**

Patients will be assigned to the celecoxib or the control group through a computer-generated randomization -
Designed by a person external to the study and otherwise unrelated to it - using by Microsoft ® Excel 2013. Participants will be assigned to the treatment groups in sequential order, and the randomization list will be confidential (randomization list maintained off-site by the study coordinator, only one person outside the study knows it). The software generates a sequence of 200 random number without repetition (1 to 200), assigning a control group code to 100 numbers and a celecoxib group code the other 100. Subsequently, the numbers generated are automatically sorted in ascending order to determine patient's allocation to one of the two study groups. Participants will be assigned to the celecoxib or the control group in sequential order once the study's coordination (the psychiatrist) verifies fulfillment of inclusion criteria.

Blinding:

Patients, the psychiatrist and the statistician will remain blinded to the identity of the two treatment groups until the end of the study. The psychiatrist assess the severity of the symptoms and keep the YMRS scores confidential in a closed envelope at every follow-up until the end of the study.

Statistical analysis

A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and 4 weekly measurements during treatment as the within-subjects factor (time) were considered; this was done for YMRS total scores. To eliminate interaction, baseline score was considered as the covariate in the analysis. The two groups at baseline were compared and the outcome of the two groups at 9, 18, and 28 days from the start of trial was also compared using an unpaired student's t-test with a two-sided P-value. The results are presented as mean ± standard deviation (SD). Data were analyzed using commercially available statistical packages (SPSS 11.5. Chicago, IL). In order to compare the demographic data and frequency of side effects between the protocols, Fisher's exact test (two-sided) was performed. All statistical tests were two-sided and were considered statistically significant at P≤0.05.

Results

Demographic characteristics

Patients (58) were initially examined, among whom 4 did not fall within the inclusion criteria and 9 were eliminated due to the exclusion criteria. Therefore, 45 patients were enrolled in the study; 23 were assigned to the Celecoxib group and 22 were assigned to the placebo group. The characteristics of the two study groups are summarized in Table 1.
|                         | Celecoxib group | placebo group | P-Value |
|-------------------------|-----------------|---------------|---------|
| **sex**                 | Female: 9(45%)  | Female: 15(75%) | 0.10   |
|                         | Male: 11(55%)   | Male: 5(25%)   |         |
| *Age                    | 30.60±8.28      | 37.90±10.59    | 0.01    |
| *Marital status        | Married: 12(60%) | Married: 12(60%) | 1.00   |
|                         | Single: 8(40%)  | Single: 8(40%) |         |
| **Number of episode**  | 2.05±1.39       | 1.70±0.92      | 0.50    |
| *Past psychiatric history | Yes: 2(10%) | Yes: 8(40%) | 0.02 |
|                         | No: 18(90%)    | No: 12(60%)    |         |
| *Past medical history  | Yes: 15(75%)   | Yes: 13(65%)   | 0.49    |
|                         | No: 5(25%)     | No: 7(35%)     |         |
| *Family history        | Yes: 11(55%)   | Yes: 9(45%)    | 0.75    |
|                         | No: 9(45%)     | No: 11(55%)    |         |

*: frequency (percent)

**: mean ±SD

There were no statistically significant differences between the groups regarding number of episode, sex, marital status, past medical history and family history. P-value ≥0.05

40 patients completed the 4-week trial, while 5 patients discontinued the trial.

Three patients from the Celecoxib group left the trial due to personal reasons unknown to the authors. One of the patients in the placebo group withdrew from the study due to vomiting and another patient discontinued the trial, because of early discharge (Figure 1)

**Efficacy: ROUTNE TREATMENT +Celecoxib vs. ROUTNE TREATMENT + Placebo**

There were no significant differences between the two groups at week 0 (baseline) on the Young Mania Rating Scale (t: 0.29, df:38, P:0.76). Table 2

Table 2: mean ±SD in two groups in the course of study
### Table

|       | group    | N  | Mean±SD     | P value |
|-------|----------|----|-------------|---------|
| Day0  | patient  | 20 | 37.1500±6.9 | 0.769   |
|       | placebo  | 20 | 36.5500±5.70 |         |
| Day9  | patient  | 20 | 30.7500±7.99 | 0.743   |
|       | placebo  | 20 | 29.8500±9.20 |         |
| Day18 | patient  | 20 | 25.9500±8.19 | 0.899   |
|       | placebo  | 20 | 26.3000±9.17 |         |
| Day28 | patient  | 20 | 21.1000±7.48 | 0.258   |
|       | placebo  | 20 | 24.0500±8.72 |         |

Percentage response was a significant difference at week 4 as compared to the baseline. In the patient group 50 % in patient group response to treatment vs 20 % in placebo group response to Celecoxib: P: 0.04. (Figure 2)

The difference between the two treatments was not significant as shown by the effect of the group; the between-subjects factor (Greenhouse–Geisser correction; df:1, F:0.38, P:0.84). The behavior of the two treatments was similar across time (groups-by-time interaction, Greenhouse–Geisser correction) F:8.17, df:1, P:0.001.figure 3

Figure show the patient group had a clinical greater reduction in YMRS scores but were not statistically significant different.

We considered Age and number of episode as a cofounding factor but the result were no changes

Effect size in this study was from 36.8 (CI95%:34.7-38.9) to 22.5 (CI95%:19.9-25.1)

**Clinical complications and side effects**

About 5 category of side effects were observed over the period of the trial. The difference between the Celecoxib and placebo groups in the frequency of side effects was not significant. In this study, the disturbances were examined and there was no significant difference between the two groups in terms of these disturbances. Table2

Table2: clinical complication and side effect in both group
|                           | Celecoxib group | Placebo group | P-value |
|---------------------------|-----------------|---------------|---------|
| Headache                  | 2(10%)          | 3(15%)        | 0.98    |
| GI disturbance            | 4(20%)          | 2(10%)        | 0.66    |
| Decrease or increase appetite | 2(10%)      | 2(10%)        | 0.99    |
| Other (Anxiety, Sexual dysfunction) | 2(10%)      | 1(5%)         | 0.98    |
| Respiratory               | 1(5%)           | 1(5%)         | 0.99    |

**Discussion**

To the best of our knowledge, this study is the second clinical 4-week study suggesting the potential use of Celecoxib as an adjuvant to therapy in the treatment of acute mania.

It has been suggested that the clinical efficacy of treatments may be enhanced by concurrent administration of agents with anti-inflammatory effects, such as Celecoxib (21). In this study in both groups of patients, a significant improvement was shown on YMRS. But the patient group had a clinical and statistical greater reduction. In addition, similar to one of the previous trials (31), number of responded patients in celecoxib group was significantly higher than placebo group. (31)

A recent meta-analysis in bipolar disorder provided evidence of increased pro-inflammatory, anti-inflammatory, and regulatory cytokines (12). Blood level of IL-6 in acute phase of mania was higher than the control group and compared to the period of remission of symptoms and manic patients with high levels of interferon-gamma was associated with more severe clinical symptoms (based on the Young Mania Scale) (13).

Because of there was one similar clinical trial research study to evaluate the efficacy of Celecoxib in alleviating symptoms of acute mania so the closest research was used by Arabzadeh et al. in 2015 which assessed the efficacy of Celecoxib adjunctive therapy for acute bipolar mania. A clinical improvement was observed in the middle of treatment and at the end of study (28).

Celecoxib has been used in several study as an anti-inflammatory (COX-2 inhibitor) agent with negligible gastrointestinal side effects(28). In addition, some researchers evaluated cytokines level and concluded that dys regulation of cytokines is the main pro inflammatory system involved in the pathogenesis of mania(29, 30). Therefore, we can conclude that the effect of celecoxib on above mentioned cytokines and pro-inflammatory pathways may be a plausible explanation for an adjuvant therapy to mood stabilizer for the treatment of acute mania.

The results of this study provide support for the enhancement of the treatment by concurrent with Celecoxib (26). Indeed, this study shows that Celecoxib as an adjuvant agent for acute mania produces
improved outcomes in the form of more reductions of symptoms of mania, higher percentage of response rate, like other studies(25). The results of this study provide statistically significant support for the enhancement of the mood stabilizer effect of the valproate sodium by concurrent treatment with Celecoxib (26). It has been suggested that Celecoxib is a potential adjunctive treatment strategy for acute mania of bipolar disorder in a trial reported by Sayyah et al. (31).

Therapy with 400 mg/day of Celecoxib was well tolerated and no clinically significant side effects were observed. The patients' clinical characteristics such as sex and number of episode, did not differ between the groups and cannot explain the differences in the therapeutic outcome.

Limitations

This study has some limitations, including the relatively small sample size and only a fixed dose of Celecoxib, should be taken into account, which shows the need for further research. Besides, as with all NSAIDs, there is a risk of gastrointestinal problems such as peptic ulcer or bleeding when taking Celecoxib, this medication has a sporadic side effect. But this side effect is still possible and the risk increases with prolonged use. Another limitation was that no specific autoantibody screening such as NMDA was used.

Declarations

Ethics approval and consent to participate:

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee at mashhad University of Medical Sciences. All participants were informed that participation is voluntary and reassured that responses would remain confidential. Informed written consent was also obtained from all participants filling in the questionnaires. Participants may withdraw from the trial at any point without any penalty and will not receive compensation for taking part.

In the study personal information about participants collected during the consent/data collection processes are stored securely

Trial registration: Iran clinical trial register: IRCT20200306046708N1.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding:
This work was a research in the Mashhad University of medical science and without any organizational financial support

**Authors’ Contribution:** Farhad Faridhosseini: study concept and design, and writing the article; Najmeh Shahini: data collection, writing the article, and final approval of the article; Ali Talaei: writing the article, data collection, and literature review; Najmeh Shahini: data collection, writing the article, and final approval of the article, Mahbobeh Eslamzadeh and Samira Ahrari: data collection, and Majid Khadem: statistical analysis, Meysam Pourgholami critical revision of the article, provision of the materials,

**Acknowledgment:**

The authors would like to thank Psychiatry and Behavioral Sciences Research Center, Ibn-e-Sina Hospital, for the voluntary participation and cooperation of all patients in the study is highly appreciated.

**Abbreviations**

Diagnostic and Statistical Manual of Mental Disorders (DSM-V)

Yung mania rating scale (YMRS)

Statistical Package for Social Sciences (SPSS)

**References**

1. Müller N, Myint A-M, Schwarz MJ. Inflammation in schizophrenia. Adv Protein Chem Struct Biol. 2012;88:49-68.

2. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biological psychiatry. 2010;67(5):446-57.

3. Müller N, Myint A-M, Schwarz MJ. Inflammatory biomarkers and depression. Neurotoxicity research. 2011;19(2):308-18.

4. Hamdani N, Tamouza R, Leboyer M. Immuno-inflammatory markers of bipolar disorder: a review of evidence. Frontiers in bioscience (Elite edition). 2011;4:2170-82.

5. Azad FJ, Talaei A, Rafatpanah H, Yousefzadeh H, Jafari R, Talaei A, et al. Association between Cytokine production and disease severity in Alzheimer's disease. Iranian Journal of Allergy, Asthma and Immunology. 2014;433-9.

6. Cerimele JM, Chwastiak LA, Dodson S, Katon WJ. The prevalence of bipolar disorder in general primary care samples: a systematic review. General hospital psychiatry. 2014;36(1):19-25.

7. Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Archives of general psychiatry. 2011;68(3):241-51.
8. Hamdani N, Doukhan R, Kurtlucan O, Tamouza R, Leboyer M. Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. Current psychiatry reports. 2013;15(9):1-8.

9. Rapoport SI, Basselin M, Kim H-W, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. Brain research reviews. 2009;61(2):185-209.

10. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? Journal of affective disorders. 2012;141(1):1-10.

11. Becking K, Boschloo L, Vogelzangs N, Haarman B, Riemersma-Van Der Lek R, Penninx B, et al. The association between immune activation and manic symptoms in patients with a depressive disorder. Translational psychiatry. 2013;3(10):e314.

12. Dickerson F, Stallings C, Origoni A, Vaughan C, Katsafanas E, Khushalani S, et al. A combined marker of inflammation in individuals with mania. PloS one. 2013;8(9):e73520.

13. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biological psychiatry. 2013;74(1):15-25.

14. Remlinger-Molenda A, Wójciak P, Michalak M, Rybakowski J. [Activity of selected cytokines in bipolar patients during manic and depressive episodes]. Psychiatry polska. 2011;46(4):599-611.

15. Bosetti F, Rintala J, Seemann R, Rosenberger T, Contreras M, Rapoport S, et al. Chronic lithium downregulates cyclooxygenase-2 activity and prostaglandin E2 concentration in rat brain. Molecular psychiatry. 2002;7(8):845-50.

16. Bosetti F, Weerasinghe GR, Rosenberger TA, Rapoport SI. Valproic acid down-regulates the conversion of arachidonic acid to eicosanoids via cyclooxygenase-1 and-2 in rat brain. Journal of neurochemistry. 2003;85(3):690-6.

17. Ghelardoni S, Tomita YA, Bell JM, Rapoport SI, Bosetti F. Chronic carbamazepine selectively downregulates cytosolic phospholipase A2 expression and cyclooxygenase activity in rat brain. Biological psychiatry. 2004;56(4):248-54.

18. Brietzke E, Scheinberg M, Lafer B. Therapeutic potential of interleukin-6 antagonism in bipolar disorder. Medical hypotheses. 2011;76(1):21-3.

19. McNamara RK, Lotrich FE. Elevated immune-inflammatory signaling in mood disorders: a new therapeutic target? Expert review of neurotherapeutics. 2012;12(9):1143-61.

20. Gitlin M. Treatment-resistant bipolar disorder. Molecular psychiatry. 2006;11(3):227-40.

21. Marazziti D, Mucci F, Fontenelle LF. Immune system and obsessive-compulsive disorder. Psychoneuroendocrinology. 2018;93:39-44.

22. Dols A, Sienaert P, van Gerven H, Schouws S, Stevens A, Kupka R, et al. The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: a review. International clinical psychopharmacology. 2013;28(6):287-96.

23. Vancampfort D, Vansteelandt K, Correll CU, Mitchell AJ, De Herdt A, Sienaert P, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. American Journal of Psychiatry. 2013.
24. Ong H, Ong L, Tan T, Chean K. Cardiovascular effects of common analgesics. The Medical journal of Malaysia. 2013;68(2):189-94.

25. Middleton R, Wheaton MG, Kayser R, Simpson HB. Treatment Resistance in Obsessive-Compulsive Disorder. Treatment Resistance in Psychiatry: Springer; 2019. p. 165-77.

26. Kaplan BJ. Kaplan and Sadock's Synopsis of Psychiatry. Behavioral Sciences/Clinical Psychiatry. Tijdschrift voor Psychiatrie. 2016;58(1):78-9.

27. Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization. 2001;79(4):373.

28. Gordo AC, Walker C, Armada B, Zhou D. Efficacy of celecoxib versus ibuprofen for the treatment of patients with osteoarthritis of the knee: A randomized double-blind, non-inferiority trial. Journal of International Medical Research. 2017;45(1):59-74.

29. Poletti S, Leone G, Hoogenboezem TA, Ghiglino D, Vai B, de Wit H, et al. Markers of neuroinflammation influence measures of cortical thickness in bipolar depression. Psychiatry Research: Neuroimaging. 2019;285:64-6.

30. Ghafelehbashi H, Pahlevan Kakhki M, Kular L, Moghbelinejad S, Ghafelehbashi S. Decreased Expression of IFNG-AS 1, IFNG and IL-1B Inflammatory Genes in Medicated Schizophrenia and Bipolar Patients. Scandinavian journal of immunology. 2017;86(6):479-85.

31. Shalbafan M, Mohammadinejad P, Shariat S-V, Alavi K, Zeinoddini A, Salehi M, et al. Celecoxib as an adjuvant to fluvoxamine in moderate to severe obsessive-compulsive disorder: a double-blind, placebo-controlled, randomized trial. Pharmacopsychiatry. 2015;48(4-5):136-40.

Figures
Figure 1

CONSORT diagram showing the disposition of all subjects screened for the study.
Figure 2

response ratio in two groups

Figure 3

response ratio in two groups
the Plot of the two groups over time