Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol do not affect 6-month mood-stabilizing treatment outcome among 482 patients with bipolar disorder

Short title: NSAIDs and mood-stabilizing treatment outcome

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Abstract:

Background

Many mood disorder patients need analgesics due to increased pain sensitivity. Recent studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may inhibit antidepressant treatment, which requires replication before clinical recommendations.

Methods

The Clinical and Health Outcomes Initiatives in Comparative Effectiveness for Bipolar Disorder Study randomized participants to 6 months lithium or quetiapine treatment. Use of NSAIDs and paracetamol was assessed throughout the study period and psychopathology measured with the Clinical Global Impression Scale for bipolar disorder (CGI-BP) and Bipolar Inventory of Symptoms Scale (BISS). The effects of NSAIDs and paracetamol on treatment outcome were examined using mixed effects linear regression adjusted for age, gender, BMI, smoking-status, exercise, and somatic diseases.

Results

Among 482 participants, 177 (36.7%) used NSAIDs and/or paracetamol during the study. NSAID and paracetamol users did not differ from non-users with respect to treatment

outcome with lithium or quetiapine at any time-point during 6 month treatment on the overall CGI-BP (β=0.001 (95%-CI=-0.01-0.01), p=0.87), the BISS (β=0.01 (95%-CI=-0.17-0.15), p=0.91), nor the CGI-BP subscales for depression or mania. Users of NSAIDs only (n=76), paracetamol only (n=62), and users of both NSAIDs and paracetamol (n=39) showed no statistical difference compared to non-users (all p>0.3).

Conclusions

This is the first trial to show that use of NSAIDs and paracetamol, alone or in combination, does not affect lithium- or quetiapine-based bipolar disorder mood-stabilizing treatment outcomes. Prior studies have suggested that NSAIDs may inhibit antidepressant treatment, whereas our results support findings indicating no detrimental effects of NSAIDs or paracetamol on affective disorder treatment.

Introduction:

Treatment outcomes in affective disorders, i.e. unipolar and bipolar depression, are often suboptimal.[1] This is further complicated by the presence of comorbid occurring somatic diseases (e.g. painful states) which have been associated with worse treatment effects.[2,3] These issues represent important clinical challenges as comorbid diseases necessitate relevant treatment, potentially leading to polypharmacy. Therefore, it is noteworthy that recent studies, including animal models and clinical data, suggested that concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may worsen the outcomes of selective serotonin reuptake inhibitor (SSRI) treatment.[4,5] However, these findings are controversial,[6] and since NSAIDs are frequently used among individuals taking SSRIs,[7] these associations represent findings with a potential impact on clinical decision-making and thus, need replication.

Interestingly, a more recent study including 811 depressed patients from the Genome-Based Therapeutics Drugs for Depression (GENDEP) trial found no change in treatment outcome among patients using NSAIDs during 12 weeks treatment with the SSRI escitalopram or the tricyclic antidepressant (TCA) nortriptyline.[8] Furthermore, two pharmacoepidemiological studies emphasized the high heterogeneity between the different

NSAIDs, indicating the safety of several frequently used NSAIDs when used in combination with SSRIs [7] or lithium. [9] Other studies have actually indicated that short-term, adjunctive NSAID treatment may yield additional antidepressant treatment effects.[10,11] Finally, it has been suggested that the findings associating NSAIDs with poorer antidepressant treatment response may be explained by confounding factors, e.g. residual confounding,[5,6] emphasizing the need for further clinical trials investigating the interaction between these frequently used drugs among patients with affective disorder.

Due to the high clinical relevance, the abovementioned associations have to be investigated in different populations of patients with affective disorders. To date, no clinical studies have investigated whether concomitant use of NSAIDs may affect treatment of patients with bipolar disorder. Thus, we prospectively investigated whether use of NSAIDs and paracetamol may affect mood-stabilizing treatment among patients with bipolar disorder in the Clinical and Health Outcomes Initiatives in Comparative Effectiveness for Bipolar Disorder Study (Bipolar CHOICE) study. This study is ideal to examine the association of NSAIDs with treatment outcomes as it was a generalizable, highly representative sample of individuals with bipolar disorder (e.g., participants were not excluded if they had comorbid medical conditions), receiving one of two pharmacotherapy intervention (lithium or quetiapine) commonly used to treat the condition with long follow-up.

Materials and Methods:

Setting

The present study represents a secondary analysis from the Bipolar CHOICE study.[12] Bipolar CHOICE was a 6-month multi-site, randomized comparative effectiveness trial, comparing lithium (a classic mood-stabilizer) to quetiapine (a commonly used antipsychotic), combined with other guideline-informed medications for bipolar disorder (but not with one another) consistent with typical clinical practice. Subjects provided verbal and written informed consent prior to participation in the presence of the study clinician. The Institutional Review Boards of the different sites approved the study protocol, and the

rationale, design and specific methods of Bipolar CHOICE are reported in detail elsewhere.[12]

Participants

For Bipolar CHOICE, 692 patients aged between 18 and 62 years were screened, whereof 482 were randomized. Limited inclusion and exclusion criteria were utilized to maximize heterogeneity of the sample and generalizability of the results, but participants were required to have a DSM-IV-TR bipolar I or bipolar II diagnosis and to be at least mildly symptomatic (Clinical Global Impression Scale for Bipolar Disorder (CGI-BP) ≥3 [13]) at study entry.

Psychiatric and substance use diagnoses were determined using the extended Mini-International Neuropsychiatric Interview, an electronic version of a validated structured diagnostic interview.[14] Psychiatric symptom severity was measured with the CGI-BP [13] and the Bipolar Inventory of Symptoms Scale (BISS).[15,16] The CGI-BP has an overall illness severity rating as well as subscales for depression and mania severity. All participants were rated with the above mentioned symptom scales at baseline as well as over the 6 month study period (i.e., 8 follow-up visit). Clinical interviews obtained demographic information and medical history.

NSAID and paracetamol use

At baseline and the 8 follow-up visits, the medication doses and dose changes were captured on the Medication Recommendation Tracking Form.[17] In agreement with prior studies,[4,5,8] we considered NSAIDs and paracetamol separately and included the same NSAID compounds: acetylsalicylic acid (aspirin), celecoxib, diclofenac, ibuprofen, naproxen, indomethacin, and meloxicam. Paracetamol included acetaminophen and its derivatives, but excluded opiates. Since NSAIDs and paracetamol often are used for short periods of time or at low dosages (e.g., acetylsalicylic acid for cardiovascular prevention), we assessed how many individuals used these compounds at significant dosages which are likely to have

anti-inflammatory and pain-relieving properties. Dosage of each drug was coded with reference to the effective dose range recommended by the World Health Organization (WHO) (http://www.whocc.no). The dose of at least the minimum recommended therapeutic dose at ≥1 visit was considered therapeutically significant, which was used in prior studies.[4,5,8] We coded individuals as users if they had used NSAIDs or paracetamol at this significant dose at any point during the study. In order to investigate the compounds in more detail, we divided users into whether they had used NSAIDs only, paracetamol only, or both NSAIDs and paracetamol.

Statistical analysis

We included baseline information on the following covariates which are likely to have an impact on treatment outcome and the propensity to receive NSAIDs or paracetamol: age, gender, body mass index (BMI), current smoking, regular exercise (i.e. at least once weekly), and the medical conditions of diabetes, hypertension and hyperlipidemia. To explore the relationship between use of NSAIDs and/or paracetamol with the above mentioned covariates, we performed logistic regression analyses and report odds ratios (OR) including 95% confidence intervals (95%-CI).

To investigate the effect of NSAID/paracetamol use on mood-stabilizing treatment outcome, we performed mixed effects linear regression models to assess differences in treatment outcome between NSAID/paracetamol users and non-users and report β-coefficients including 95%-CI. These models allow inclusion of all relevant covariates across repeated measurements and efficiently handle missing data.[18] We compared users of NSAIDs/paracetamol with non-users on the overall treatment effect after 6 months and on the treatment effect at every visit during the study period. The dependent variables were the total scores on the included rating scales (overall CGI-BP, BISS, CGI-BP subscales for depression and mania) at up to 9 assessments (i.e., baseline and 8 follow-up visits) during the 6 month study period. We performed all analyses in an unadjusted model and also in a model adjusting for all covariates to distinguish whether an effect of NSAIDs or paracetamol on treatment outcome may be due to the NSAIDs or other factors resulting in the use of NSAIDs.

For the primary analyses, we investigated whether individuals with use of NSAIDs or paracetamol differed from non-users on the overall treatment outcome, measured by the overall CGI-BP, the CGI-BP subscales for depression and mania, and the BISS scale. Secondary analyses comprised all analyses among individuals randomized to lithium respectively quetiapine. Third, to be able to distinguish between NSAIDs and paracetamol in more detail, we performed analyses among individuals using NSAIDs only, individuals using paracetamol only, and individuals using both NSAIDs and paracetamol, all compared to non-users. Finally, we performed interaction analyses between NSAID/paracetamol use and the two treatment regimens (i.e., lithium and quetiapine) to further explore differences between the two study drugs. All analyses were performed using STATA 14.0.

Sensitivity analyses

First, we performed age and gender specific analyses. Secondly, since painful states (the indication for NSAID and paracetamol treatment) often are accompanied by inflammatory processes, we included the baseline white blood cell count (WBC). At study entry, a fasting blood draw assessed WBC, expressed in International units, i.e. $x10^9$/L. A WBC measure $\geq 10x10^9$/L (i.e., leukocytosis), indicates an inflammatory response. We investigated whether NSAID/paracetamol use changed treatment outcome among individuals with a baseline WBC $\geq 10x10^9$/L respectively among individuals with a baseline WBC $<10x10^9$/L. Third, we performed sensitivity among lithium users who were treated within the therapeutic range (0.6-1.2 mMol/L) during the study period. Finally, the main analyses included non-users with missing data concerning co-medication at ≥1 study visits (N=105 (34.4%) out of the 305 non-users), and we investigated whether the exclusion of the non-users with missing data affected our results.

Results

Among 482 Bipolar CHOICE participants, 177 (36.7%) used NSAIDs or paracetamol during the study period, (76 (15.8%) used NSAIDs only, 62 (12.8%) used paracetamol only, and 39 (8.1%) used both NSAIDs and paracetamol). The baseline characteristics of

NSAID/paracetamol users and non-users are depicted in Table 1. When investigating the relationship between NSAID/paracetamol use and potential confounders, we found that users, compared to non-users, were more likely to be female and to have a diagnosis of hypertension, but less likely to have a diagnosis of diabetes.

Effect of NSAID and/or paracetamol use on mood-stabilizing treatment outcome

A total of 382 patients completed all 9 study visits. During 6 months of mood-stabilizing treatment, the fully adjusted mixed effects linear regression models showed that all 482 participants decreased in overall CGI-BP by a β-coefficient of -0.05 per week (95%-CI=-0.06; -0.04) (Table 2). Users of NSAIDs or paracetamol decreased in overall CGI-BP by a β of -0.052 per week (95%-CI=-0.06; -0.044), whereas non-users decreased by a β of -0.051 per week (95%-CI=-0.058; -0.044). All results were significant ($p<0.001$). When comparing users of NSAIDs or paracetamol to non-users regarding the decrease in overall CGI-BP, we found no difference as indicated by a β of -0.001 (95%-CI=-0.01; 0.01), $p=0.87$). Furthermore, we found no differences between users and non-users on the BISS (β=0.01, 95%-CI=-0.17; 0.15, $p=0.91$) nor on the CGI-BP subscales for depression ($p=0.86$) or mania ($p=0.51$). In addition, we found no significant differences between NSAID/paracetamol users and non-users at any time point during the 6 month follow-up (Figure 1). All the above mentioned results were similar in the unadjusted models (results not shown).

Second, we investigated whether NSAID/paracetamol treatment affected the specific mood-stabilizing treatment to confirm the above mentioned negative results. When comparing NSAID/paracetamol users to non-users, we found that there was not a different treatment response among 240 individuals randomized to lithium or among 242 individuals randomized to quetiapine, as tested with the overall CGI-BP, BISS, and CGI-BP subscales for depression and mania (all $p>0.05$ as shown in Table 3). During 6 month of treatment with lithium respectively quetiapine, we found no significant differences between NSAID/paracetamol users and non-users at any time point on the CGI-BP or on the BISS (Figure 1). Furthermore, we performed interaction analyses between NSAID/paracetamol use and treatment arm (i.e., lithium or quetiapine), emphasizing no differences in treatment

response as measured with the overall CGI-BP (p=0.53) and the BISS (p=0.42). The unadjusted models showed very similar results (results not shown).

NSAIDs only, paracetamol only, and the combination of NSAIDs and paracetamol

To further investigate the effects of the specific compounds, we performed analyses among individuals using NSAIDs only (N=76), individuals using paracetamol only (N=62), and individuals using both NSAIDs and paracetamol (N=39). Compared to non-users of NSAIDs or paracetamol, we found no significant difference in 6 month treatment outcome for these subgroups on the overall CGI-BP and BISS or on the CGI-BP subscales for depression or mania (Table 4). In addition, within these three subgroups, we found no significant differences among individuals randomized to lithium or quetiapine, or at any time point during the 6 month study period (all p>0.05, results not shown).

Sensitivity analyses

We found no differences in age-specific or gender separate analyses (all p>0.05, results not shown). In addition, use of NSAIDs and/or paracetamol did not affect lithium or quetiapine treatment among 50 individuals with a baseline WBC≥$10x10^9$/L, indicating an inflammatory response, or among 432 individuals with a baseline WBC<$10x10^9$/L (all p>0.05, results not shown). Furthermore, of the 240 individuals randomized to lithium, a total of 104 (43.3%) were within therapeutic ranges during the study period, whereof 45 (43.2%) used NSAIDs or paracetamol. Analyses on this subgroup (N=104) showed no differences in treatment effects between users and non-users of NSAIDs/paracetamol with no differences at any time point during the 6 month study period (all p>0.05, results not shown). Finally, we found no significant differences between NSAID/paracetamol users and non-users after exclusion of the 105 non-users with missing data regarding co-medication (all p>0.05, results not shown).

Discussion

NSAIDs and paracetamol are among the most frequently used drugs among individuals with affective disorders due to somatic comorbidity and increased pain sensitivity.[7] The present study represents the first trial investigating whether NSAIDs and paracetamol negatively affect mood-stabilizing treatment in bipolar disorder. We have attempted to replicate findings from previous studies that reported conflicting results regarding the safety of NSAIDs and paracetamol during antidepressant treatment.[4,5,8] Within the Bipolar CHOICE trial including 482 patients with bipolar disorder, use of NSAIDs and paracetamol, compared to non-use, was not associated with differing treatment outcomes of mood-stabilizing treatment. Individuals using NSAIDs and/or paracetamol (N=177; 36.7%) were more likely to be female and differed regarding somatic comorbidity. Despite these differences, NSAIDs and paracetamol, used alone or in combination with each other, did not affect treatment outcome with lithium or quetiapine at any time during the 6 month follow up period. The results were similar in the unadjusted and adjusted models. This finding is particularly noteworthy as we only included NSAID and paracetamol at therapeutic pain-relieving doses, used different symptom scales as possible outcomes, adjusted for important covariates, and conducted several sub-analyses. Hence, our results support findings [8,9] suggesting the safety of NSAIDs and paracetamol among individuals treated for their affective disorder. Since the Bipolar CHOICE study was a pragmatic trial designed to maximize generalizability, our results are relevant and representative for everyday clinical work.

Effects of NSAIDs and paracetamol on treatment of affective disorders

Given that pain-related somatic comorbidity is common in mood disorders requiring the need for pain-relieving medications, it is important to examine the potential beneficial or harmful combination of NSAIDS and psychiatric medications in clinical trials. Recent studies included animal models and clinical data to investigate whether use of NSAIDs affects SSRI treatment.[4,5] The results associated NSAIDs with worse outcomes of SSRI treatment, and the authors concluded that “clinicians should carefully balance the therapeutic benefits of antiinflammatory agents versus the potentially negative consequences of antagonizing the therapeutic efficacy of antidepressant agents in patients suffering from depression”.[4] However, these findings have not been replicated in other clinical trials or patients with

other affective disorders, thus requiring caution concerning clinical recommendations. Indeed, within the GENDEP study, NSAID use was not associated with different treatment effects among 811 patients with depression.[8] The authors found no differences in treatment outcome among individuals randomized to 12 weeks treatment with the SSRI escitalopram or the tricyclic antidepressant (TCA) nortriptyline. Furthermore, a pharmacoepidemiological study found that NSAID use during lithium treatment was not associated with clinical deterioration.[9] Finally, Gallagher et al. suggested that their results associating NSAIDs with poorer antidepressant effects might be due to confounding factors, emphasizing cautiousness, particularly regarding clinical recommendations based on their results.[5] This cautiousness has also been emphasized by other researchers.[6]

Other studies have actually indicated that targeted short-term NSAID treatment may improve the treatment outcomes when used as add-on to antidepressants [19] or mood-stabilizers.[10] Indeed, it has been discussed that specific subgroups of patients with affective disorders, e.g. those with increased pro-inflammatory biomarkers, may benefit of additional NSAID treatment.[11,20,21]

Despite these potential beneficial treatment effects in specific subgroups, the far more frequent occurring clinical challenge is the need for pain-relieving treatment because of comorbid somatic states. Therefore, it is important that our results support previous findings [8] suggesting that NSAIDs and paracetamol does not negatively impact the treatment of affective disorders. Nevertheless, NSAIDs have been associated with side effects, such as an increased risk for gastrointestinal bleeding [22] and cardiovascular events.[23] Hence, clinicians should always balance the beneficial pain-relieving effects of NSAIDs and paracetamol against the risk for side effects for each patient individually.

Strengths and limitations

The Bipolar CHOICE study was a pragmatic trial designed to maximize generalizability, thus representing patients with bipolar disorder seen in everyday clinical practice. In addition, we were able to adjust for age, gender, BMI, smoking-status, exercise, and specific somatic diseases, all representing important covariates affecting treatment outcome and the

propensity for receiving NSAIDs and paracetamol. Furthermore, NSAID and paracetamol use was identified at every study visit,[17] minimizing the risk for missing the use of these compounds, i.e. minimizing the risk for misclassification. Finally, the definition of NSAID and paracetamol use, including the analytical approaches, were in agreement with prior studies investigating this aspect [4,5,8] highlighting the comparability of our findings.

Our findings should also be considered within the limitations of this study. First, with a larger sample size it would have been possible to detect potential small effect sizes. Second, we did not measure all possible confounding variables, although we did include several clinically relevant covariates. For example, we had no measure on chronic pain symptoms, which could influence both NSAID use and treatment outcome. Third, patients with bipolar disorder often require treatment for several years and the study period of 6 months in the present study limited our ability to address longer-term effects. Finally, data were collected within the context of a randomized study which does reduce the generalizability of these data despite our efforts to mimic real-world patients by having very few inclusion and exclusion criteria.

Conclusion

Among 482 participants from the Bipolar CHOICE study, a total of 177 (37%) used NSAIDs and/or paracetamol at therapeutic doses during 6 month treatment with lithium or quetiapine. Use of NSAIDs and paracetamol, alone or in combination, did not affect lithium or quetiapine treatment response at any time point during the 6 month mood-stabilizing treatment. Thus, the present study is the first to investigate this clinically important aspect among patients with bipolar disorder, and our results support prior findings suggesting that use of NSAIDs and paracetamol does not inhibit the efficacy of psychotropic treatment in affective disorders. The clinical importance of our findings is further emphasized since these compounds are among the most frequently used medications among patients with affective disorders due to the high prevalence of somatic comorbidity and by the generalizability of the Bipolar CHOICE trial.

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Conflicts of interest:

Dr. Sylvia was a shareholder in Concordant Rater Systems and has served in the past year as a consultant for United Biosource Corporation, Clintara, Bracket, and Clinical Trials Network and Institute. Dr. Sylvia receives royalties from New Harbinger. She has received grant/research support from NIMH, PCORI, AFSP, and Takeda.

Dr. Thase has been an advisor/consultant: to Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck, MedAvante, Merck, Mylan, Neuronetics, Otsuka, Pamlab, PharmaNeuroboost, Pfizer, Rexahn, Roche, Shire, Sunovion, Supernus, Takeda, and Teva, as well as the US Food and Drug Administration and the National Institute of Mental Health. During the same time frame, Dr Thase has received honoraria for talks from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, and Pfizer and he has received research grants from Alkermes, AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Otsuka, PharmaNeuroboost, and Roche, as well as the National Institute of Mental Health and the AHRQ.

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Dr. Tohen was a full time employee at Lilly (1997 to 2008). He has received honoraria from, or consulted for, Abbott, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Lilly, Johnson & Johnson, Otsuka, Merck, Sunovion, Forest, Geodon Richter Plc, Roche, Elan, Alkermes, Allergan, Lundbeck, Teva, Pamlab, Wyeth and Wiley Publishing. His spouse was a full time employee at Lilly (1998-2013).

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Between May 14, 2010 to present, **Dr. Ketter** had the following financial interests/arrangements or affiliations that could be perceived as real or apparent conflicts of interest: grant/research support from Agency for Healthcare Research and Quality, AstraZeneca Pharmaceuticals LP, Cephalon Inc. (now Teva Pharmaceuticals), Eli Lilly and Company, Pfizer, Inc., Merck & Co., Inc., and Sunovion Pharmaceuticals; consultant/advisory board fees from Acadia Pharmaceuticals, Allergan, Inc., Avanir Pharmaceuticals, Depotmed, Forest Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Merck & Co., Inc., ProPhase, Sunovion Pharmaceuticals, Teva Pharmaceuticals, Bristol-Myers Squibb Company and Cephalon, Inc; lecture honoraria from Abbott Laboratories, Inc., GlaxoSmithKline, Otsuka Pharmaceuticals, Pfizer, Inc., and AstraZeneca Pharmaceuticals LP; and royalties from American Psychiatric Publishing, Inc. In addition, Dr. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals.

Dr. McElroy is a consultant to or member of the scientific advisory boards of Bracket, F. Hoffmann-La Roche Ltd., MedAvante, Naurex, Novo Nordisk, Shire, and Sunovion. She is a principal or co-investigator on studies sponsored by the Agency for Healthcare Research & Quality (AHRQ), Alkermes, Cephalon, Forest, Marriott Foundation, National Institute of Mental Health, Naurex, Orexigen Therapeutics, Inc., Shire, and Takeda Pharmaceutical Company Ltd. She is also an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent.

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References

1. Nierenberg AA. Strategies for achieving full remission when first-line antidepressants are not enough. *J Clin Psychiatry*. 2013;74(12):e26. doi: 10.4088/JCP.13018tx3c [doi].

2. Iosifescu DV, Bankier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. *Curr Psychiatry Rep*. 2004;6(3):193-201.

3. Sylvia LG, Shelton RC, Kemp DE, et al. Medical burden in bipolar disorder: Findings from the clinical and health outcomes initiative in comparative effectiveness for bipolar disorder study (bipolar CHOICE). *Bipolar Disord*. 2015;17(2):212-223. doi: 10.1111/bdi.12243 [doi].

4. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. *Proc Natl Acad Sci U S A*. 2011;108(22):9262-9267. doi: 10.1073/pnas.1104836108; 10.1073/pnas.1104836108.

5. Gallagher PJ, Castro V, Fava M, et al. Antidepressant response in patients with major depression exposed to NSAIDs: A pharmacovigilance study. *Am J Psychiatry*. 2012;169(10):1065-1072.

6. Shelton RC. Does concomitant use of NSAIDs reduce the effectiveness of antidepressants? *Am J Psychiatry*. 2012;169(10):1012-1015. doi: 10.1176/appi.ajp.2012.12070924 [doi].

7. Kohler O, Petersen L, Mors O, Gasse C. Inflammation and depression: Combined use of selective serotonin reuptake inhibitors and NSAIDs or paracetamol and psychiatric outcomes. *Brain Behav*. 2015;5(8):e00338. doi: 10.1002/brb3.338 [doi].

8. Uher R, Carver S, Power RA, et al. Non-steroidal anti-inflammatory drugs and efficacy of antidepressants in major depressive disorder. *Psychol Med*. 2012;42(10):2027-2035.

9. Stolk P, Souverein PC, Wilting I, et al. Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder. *Prostaglandins Leukotrienes Essent Fatty Acids*. 2010;82(1):9-14.

10. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: A double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol*. 2008;23(2):87-94.

11. Kohler 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. *JAMA Psychiatry*. 2014;71(12):1381-1391. doi: 10.1001/jamapsychiatry.2014.1611 [doi].

12. Nierenberg AA, Sylvia LG, Leon AC, et al. Clinical and health outcomes initiative in comparative effectiveness for bipolar disorder (bipolar CHOICE): A pragmatic trial of complex treatment for a complex disorder. *Clin Trials*. 2014;11(1):114-127. doi: 10.1177/1740774513512184 [doi].

13. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the clinical global impressions (CGI) scale for use in bipolar illness (BP): The CGI-BP. *Psychiatry Res*. 1997;73(3):159-171. doi: S0165-1781(97)00123-6 [pii].

14. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.

15. Bowden CL, Singh V, Thompson P, et al. Development of the bipolar inventory of symptoms scale. *Acta Psychiatr Scand*. 2007;116(3):189-194. doi: ACP955 [pii].

16. Gonzalez JM, Bowden CL, Katz MM, et al. Development of the bipolar inventory of symptoms scale: Concurrent validity, discriminant validity and retest reliability. *Int J Methods Psychiatr Res*. 2008;17(4):198-209. doi: 10.1002/mpr.262 [doi].

17. Reilly-Harrington NA, Sylvia LG, Leon AC, et al. The medication recommendation tracking form: A novel tool for tracking changes in prescribed medication, clinical decision making, and use in comparative effectiveness research. *J Psychiatr Res*. 2013;47(11):1686-1693. doi: 10.1016/j.jpsychires.2013.07.009 [doi].

18. Lane P. Handling drop-out in longitudinal clinical trials: A comparison of the LOCF and MMRM approaches. *Pharm Stat*. 2008;7(2):93-106. doi: 10.1002/pst.267 [doi].

19. Muller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: Results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry*. 2006;11(7):680-684.

20. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 2013;70(1):31-41.

21. Rapaport MH, Nierenberg AA, Schettler PJ, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: A proof-of-concept study. *Mol Psychiatry*. 2016;21(1):71-79. doi: 10.1038/mp.2015.22 [doi].

22. de Abajo FJ, Garcia-Rodriguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: Interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry*. 2008;65(7):795-803. doi: 10.1001/archpsyc.65.7.795; 10.1001/archpsyc.65.7.795.

23. Schjerning Olsen AM, Fosbol EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: A nationwide cohort study. *Circulation*. 2011;123(20):2226-2235. doi: 10.1161/CIRCULATIONAHA.110.004671; 10.1161/CIRCULATIONAHA.110.004671.

Figure 1 CGI-BP and BISS scores during 6 months of follow-up* among 240 individuals randomized to lithium (top two figures) respectively 242 individuals randomized to quetiapine (bottom two figures). Lithium (N = 240, whereof N = 98 (40.8%) used NSAIDS or paracetamol.
There were no significant differences between users of NSAIDs/paracetamol and non-users at any time point (all p > 0.05). Abbreviations: CGI-BP= Clinical Global Impression for Bipolar Disorder; BISS= Bipolar Inventory Symptom Scale; NSAID= Non-steroidal anti-inflammatory drug.
*All mixed effects linear regression analyses were adjusted for: age, gender, body mass index (BMI), current smoking, regular exercise (i.e. at least once weekly), and the medical conditions of diabetes, hypertension and hyperlipidemia.

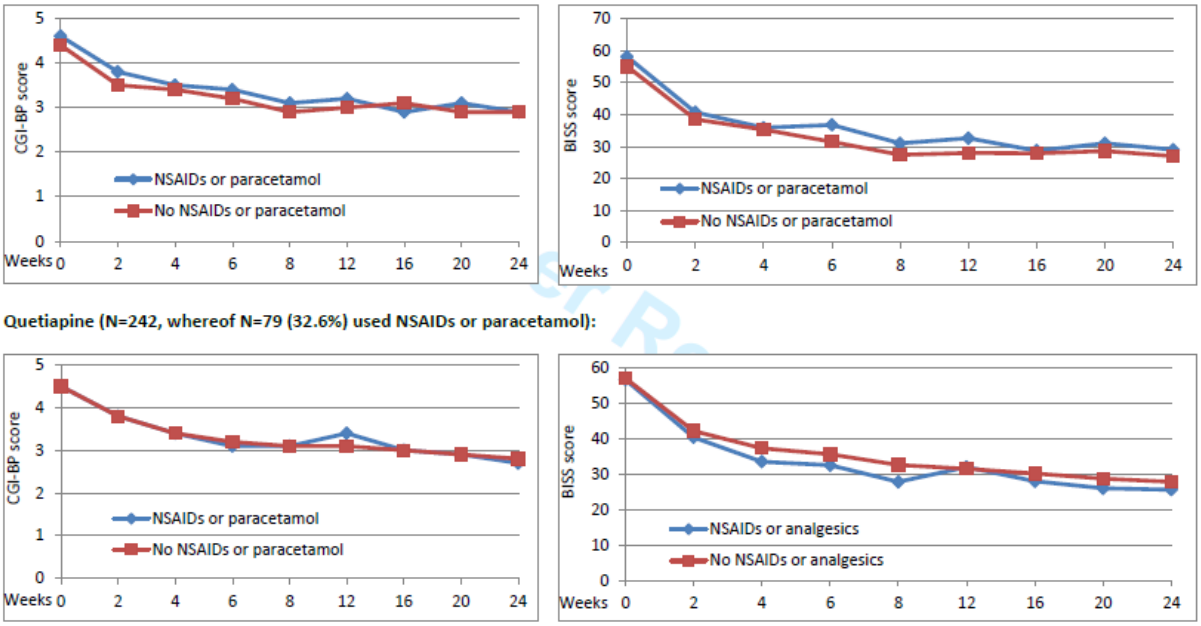

Table 1: Baseline information for 482 patients with bipolar disorder, divided into non-users[1] and users[1] of NSAIDs or paracetamol.

	Total	Non-users of NSAIDs or paracetamol[1]	Users of NSAIDs or Paracetamol[1]	Users vs. non-users[2] OR (95%-CI)
Total	482 (100)	305 (63.3)	177 (36.7)	

Gender				
Male	199 (41.3)	139 (45.6)	60 (33.9)	1.0 (ref.)
Female	283 (58.7)	166 (54.4)	117 (66.1)	**1.84 (1.15; 2.93)**
Mean Age (IQR)	38.9 (28; 49)	38.2 (28; 47)	40.1 (30; 50)	
Age-group				
≤30	153 (31.7)	105 (34.4)	48 (27.1)	1.0 (ref.)
31-45	167 (34.7)	103 (33.8)	64 (36.2)	1.13 (0.63; 2.03)
≥45	162 (33.6)	97 (31.8)	65 (36.7)	1.06 (0.58; 1.93)
Current smoking				
No	233 (48.3)	155 (50.8)	78 (27.7)	1.0 (ref.)
Yes	249 (51.7)	150 (49.2)	99 (72.3)	1.15 (0.69; 1.91)
Weekly exercise				
No	195 (40.2)	118 (38.5)	77 (43.2)	1.0 (ref.)
Yes	287 (59.8)	187 (61.5)	100 (56.8)	0.89 (0.56; 1.42)
BMI				
<20	25 (5.2)	16 (5.3)	9 (5.1)	1.0 (ref.)
20-24.99	107 (22.2)	65 (21.5)	42 (23.9)	1.11 (0.39; 3.14)
25-29.99	134 (27.8)	90 (29.8)	44 (25.0)	0.65 (0.23; 1.85)
≥30	212 (44.0)	131 (43.4)	81 (46.0)	0.92 (0.34; 2.52)
Medical conditions				
Diabetes	30 (6.2)	21 (6.9)	9 (5.1)	**0.24 (0.07; 0.80)**
Hypertension	90 (18.7)	44 (14.4)	46 (26.0)	**1.96 (1.06; 3.63)**
Hyperlipidemia	103 (21.4)	56 (18.4)	47 (26.6)	1.29 (0.71; 2.32)
Diagnoses				
Current manic episode	33 (6.8)	22 (7.2)	11 (6.2)	0.61 (0.19; 1.94)
Current hypomanic episode	23 (4.8)	14 (4.6)	9 (5.1)	2.36 (0.64; 8.69)
Current depressive episode	303 (62.9)	185 (60.7)	118 (66.7)	1.09 (0.55; 2.14)

Current mixed episode	48 (10.0)	35 (11.5)	13 (7.3)	0.65 (0.25; 1.71)
None of the above (subthreshold)	75 (15.6)	49 (16.1)	26 (14.7)	0.90 (0.53; 1.50)

Abbreviations: NSAID: Non-steroidal anti-inflammatory drug.

[1] Users are individuals who used NSAIDs or paracetamol at significant dosages at ≥1 visit during the follow-up period.

[2] We performed logistic regression analyses comparing users of NSAIDs and/or paracetamol versus non-users and included all the covariates mentioned in Table 1 in the final model. We report odds ratios (OR) including 95% confidence intervals (95%-CI).

Table 2: Effect of additional use[1] of NSAIDs or paracetamol versus non-users[1] during 24 weeks of mood-stabilizing treatment: results of mixed effects linear regression analyses[2].

	Baseline			Estimated change per week			Estimated difference
	Total	**Non-users[1]**	**Users[1]**	**Total**	**Non-users[1]**	**Users[1]**	**Users[1] vs. non-users[1]**
	Mean ± SD	Mean ± SD	Mean ± SD	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value
NSAIDs or paracetamol (N=177)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.5 ± 0.8	-0.05 (-0.06; -0.04), p<0.001	-0.051 (-0.058; -0.044), p<0.001	-0.052 (-0.060; -0.044), p<0.001	-0.001 (-0.01; 0.01), p=0.87
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.4 ± 1.1	-0.05 (-0.06; -0.04), p<0.001	-0.049 (-0.056; -0.042), p<0.001	-0.05 (-0.059; -0.041), p<0.001	-0.001 (-0.012; 0.01), p=0.86
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.1 ± 1.1	-0.03 (-0.035; -0.025), p<0.001	-0.029 (-0.035; -0.022), p<0.001	-0.032 (-0.039; -0.025), p<0.001	-0.003 (-0.013; 0.006), p=0.51
BISS	56.6 ± 19.2	56.2 ± 20.1	57.4 ± 17.4	-0.87 (-0.96; -0.78), p<0.001	-0.88 (-0.99; -0.77), p<0.001	-0.87 (-1.00; -0.73), p<0.001	0.01 (-0.17; 0.15), p=0.91

Abbreviations: β: Regression coefficient; 95%-CI: 95% Confidence Interval; SD: Standard deviation; CGI-BP = Clinical Global Impression Scale for Bipolar Disorder; NSAID: Non-steroidal anti-inflammatory drug; BISS: Bipolar Inventory of Symptoms Scale.

A negative β indicates better treatment effect among users of NSAIDs or paracetamol, whereas a positive β indicates better treatment effect among non-users.

[1] Users are individuals who used NSAIDs or paracetamol at significant dosages at ≥1 visit during the follow-up period.

[2] All analyses were adjusted for: age, gender, body mass index (BMI), current smoking, regular exercise (i.e. at least once weekly), and the medical conditions of diabetes, hypertension and hyperlipidemia.

Table 3: Effect of additional use[1] of NSAIDs or paracetamol versus non-users[1] during 24 weeks of treatment among individuals randomized to lithium or quetiapine: results of mixed effects linear regression analyses[2].

	Lithium (n = 240)		Quetiapine (n = 242)	
	β (95%-CI)	p-value	β (95%-CI)	p-value
CGI-BP overall	-0.007 (–0.031; 0.016)	0.53	–0.008 (–0.036; 0.019)	0.56
CGI-BP depression	–0.0055 (–0.030; 0.019)	0.66	–0.020 (–0.049; 0.0097)	0.19
CGI-BP mania	–0.016 (–0.038; 0.0056)	0.15	0.007 (–0.019; 0.033)	0.60
BISS	–0.18 (–0.58; 0.23)	0.39	–0.27 (–0.74; 0.19)	0.25

Abbreviations: β: Regression coefficient; 95%-CI: 95% Confidence Interval; CGI-BP = Clinical Global Impression Scale for Bipolar Disorder; NSAID: Non-steroidal anti-inflammatory drug; BISS: Bipolar Inventory of Symptoms Scale.

A negative β indicates better treatment effect among users of NSAIDs or paracetamol, whereas a positive β indicates better treatment effect among non-users.

[1] Users are individuals who used NSAIDs or paracetamol at significant dosages at ≥1 visit during the follow-up period.

[2] All analyses were adjusted for: age, gender, body mass index (BMI), current smoking, regular exercise (i.e. at least once weekly), and the medical conditions of diabetes, hypertension and hyperlipidemia.

Table 4: Effect of additional use[1] of NSAIDs only, paracetamol only, or the combination versus non-users[1] during 24 weeks of mood-stabilizing treatment: results of mixed effects linear regression analyses[2].

	Baseline	Estimated change per week	Estimated

							difference
	Total	**Non-users[1]**	**Users[1]**	**Total**	**Non-users[1]**	**Users[1]**	**Users[1] vs. non-users[1]**
	Mean ± SD	Mean ± SD	Mean ± SD	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value
NSAIDs only (N = 76)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.5 ± 0.9	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.055 (-0.07; -0.04), p < 0.001	-0.006 (-0.022; 0.011), p = 0.49
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.3 ± 1.1	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.07; -0.04), p < 0.001	-0.005 (-0.023; 0.13), p = 0.58
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	2.9 ± 1.1	-0.03 (-0.035; -0.025), p < 0.001	-0.03 (-0.037; -0.021), p < 0.001	-0.03 (-0.045; -0.02), p < 0.001	-0.003 (-0.02; 0.13), p = 0.67
BISS	56.6 ± 19.2	56.2 ± 20.1	54.4 ± 19.8	-0.87 (-0.96; -0.78), p < 0.001	-0.87 (-1.01; -0.73), p < 0.001	-0.86 (-1.09; -0.63), p < 0.001	0.003 (-0.29; 0.29), p = 0.98
Paracetamol only (N=62)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.03), p < 0.001	0.006 (-0.012; 0.24), p = 0.49
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.3 ± 1.1	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.04 (-0.06; -0.02), p < 0.001	0.009 (-0.01; 0.28), p = 0.36
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.2 ± 1.1	-0.03 (-0.035; -0.025), p < 0.001	-0.03 (-0.037; -0.021), p < 0.001	-0.035 (-0.048; -0.021), p < 0.001	-0.005 (-0.022; 0.12), p = 0.59
BISS	56.6 ± 19.2	56.2 ± 20.1	57.5 ± 15.3	-0.87 (-0.96; -0.78), p < 0.001	-0.87 (-1.01; -0.73), p < 0.001	-0.74 (-0.99; -0.48), p < 0.001	0.16 (-0.14; 0.47), p = 0.30
NSAIDs and paracetamol (N = 39)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.03), p < 0.001	0.0003 (-0.02; 0.02), p = 0.97
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.6 ± 0.9	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.07; -0.03), p < 0.001	-0.003 (-0.025; 0.018), p = 0.75
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.2 ± 1.1	-0.03 (-0.035; -0.025), p <	-0.03 (-0.037; -0.021), p <	-0.03 (-0.048; -0.018), p <	-0.006 (-0.026; 0.014), p =

				0.001	0.001	0.001	0.56
BISS	56.6 ± 19.2	56.2 ± 20.1	63.2 ± 14.4	-0.87 (-0.96; -0.78), p < 0.001	-0.87 (-1.00; -0.73), p < 0.001	-0.96 (-1.24; -0.68), p < 0.001	-0.11 (-0.46; 0.24), p = 0.54

Abbreviations: β: Regression coefficient; 95%-CI: 95% Confidence Interval; SD: Standard deviation; CGI-BP = Clinical Global Impression Scale for Bipolar Disorder; NSAID: Non-steroidal anti-inflammatory drug; BISS: Bipolar Inventory of Symptoms Scale.
A negative β indicates better treatment effect among users of NSAIDs or paracetamol, whereas a positive β indicates better treatment effect among non-users.
[1] Users are individuals who used NSAIDs or paracetamol at significant dosages at ≥1 visit during the follow-up period.
[2] All analyses were adjusted for: age, gender, body mass index (BMI), current smoking, regular exercise (i.e. at least once weekly), and the medical conditions of diabetes, hypertension and hyperlipidemia.

	Total	Non-users of NSAIDs or paracetamol[1]	Users of NSAIDs or Paracetamol[1]	Users vs. non-users[2] OR (95%-CI)
Total	482 (100)	305 (63.3)	177 (36.7)	
Gender				
Male	199 (41.3)	139 (45.6)	60 (33.9)	1.0 (ref.)
Female	283 (58.7)	166 (54.4)	117 (66.1)	**1.84 (1.15; 2.93)**
Mean Age (IQR)	38.9 (28; 49)	38.2 (28; 47)	40.1 (30; 50)	
Age-group				
≤30	153 (31.7)	105 (34.4)	48 (27.1)	1.0 (ref.)
31-45	167 (34.7)	103 (33.8)	64 (36.2)	1.13 (0.63; 2.03)
≥45	162 (33.6)	97 (31.8)	65 (36.7)	1.06 (0.58; 1.93)
Current smoking				
No	233 (48.3)	155 (50.8)	78 (27.7)	1.0 (ref.)
Yes	249 (51.7)	150 (49.2)	99 (72.3)	1.15 (0.69; 1.91)
Weekly exercise				
No	195 (40.2)	118 (38.5)	77 (43.2)	1.0 (ref.)
Yes	287 (59.8)	187 (61.5)	100 (56.8)	0.89 (0.56; 1.42)
BMI				
<20	25 (5.2)	16 (5.3)	9 (5.1)	1.0 (ref.)

20-24.99	107 (22.2)	65 (21.5)	42 (23.9)	1.11 (0.39; 3.14)
25-29.99	134 (27.8)	90 (29.8)	44 (25.0)	0.65 (0.23; 1.85)
≥30	212 (44.0)	131 (43.4)	81 (46.0)	0.92 (0.34; 2.52)
Medical conditions				
Diabetes	30 (6.2)	21 (6.9)	9 (5.1)	**0.24 (0.07; 0.80)**
Hypertension	90 (18.7)	44 (14.4)	46 (26.0)	**1.96 (1.06; 3.63)**
Hyperlipidemia	103 (21.4)	56 (18.4)	47 (26.6)	1.29 (0.71; 2.32)
Diagnoses				
Current manic episode	33 (6.8)	22 (7.2)	11 (6.2)	0.61 (0.19; 1.94)
Current hypomanic episode	23 (4.8)	14 (4.6)	9 (5.1)	2.36 (0.64; 8.69)
Current depressive episode	303 (62.9)	185 (60.7)	118 (66.7)	1.09 (0.55; 2.14)
Current mixed episode	48 (10.0)	35 (11.5)	13 (7.3)	0.65 (0.25; 1.71)
None of the above (subthreshold)	75 (15.6)	49 (16.1)	26 (14.7)	0.90 (0.53; 1.50)

	Baseline			Estimated change per week			Estimated difference
	Total	**Non-users[1]**	**Users[1]**	**Total**	**Non-users[1]**	**Users[1]**	**Users[1] vs. non-users[1]**
	Mean ± SD	Mean ± SD	Mean ± SD	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value
NSAIDs or paracetamol (N=177)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.5 ± 0.8	-0.05 (-0.06; -0.04), p<0.001	-0.051 (-0.058; -0.044), p<0.001	-0.052 (-0.060; -0.044), p<0.001	-0.001 (-0.01; 0.01), p=0.87
CGI-BP	4.2 ± 1.1	4.2 ± 1.2	4.4 ± 1.1	-0.05 (-0.06; -0.04),	-0.049 (-0.056; -	-0.05 (-0.059; -0.041),	-0.001 (-0.012; 0.01),

depression				p<0.001	0.042), p<0.001	p<0.001	p=0.86
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.1 ± 1.1	-0.03 (-0.035; -0.025), p<0.001	-0.029 (-0.035; -0.022), p<0.001	-0.032 (-0.039; -0.025), p<0.001	-0.003 (-0.013; 0.006), p=0.51
BISS	56.6 ± 19.2	56.2 ± 20.1	57.4 ± 17.4	-0.87 (-0.96; -0.78), p<0.001	-0.88 (-0.99; -0.77), p<0.001	-0.87 (-1.00; -0.73), p<0.001	0.01 (-0.17; 0.15), p=0.91

	Lithium (n = 240)		Quetiapine (n = 242)	
	β (95%-CI)	p-value	β (95%-CI)	p-value
CGI-BP overall	-0.007 (–0.031; 0.016)	0.53	–0.008 (–0.036; 0.019)	0.56
CGI-BP depression	–0.0055 (–0.030; 0.019)	0.66	–0.020 (–0.049; 0.0097)	0.19
CGI-BP mania	–0.016 (–0.038; 0.0056)	0.15	0.007 (–0.019; 0.033)	0.60
BISS	–0.18 (–0.58; 0.23)	0.39	–0.27 (–0.74; 0.19)	0.25

	Baseline			Estimated change per week			Estimated difference
	Total	**Non-users[1]**	**Users[1]**	**Total**	**Non-users[1]**	**Users[1]**	**Users[1] vs. non-users[1]**
	Mean ± SD	Mean ± SD	Mean ± SD	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value	β (95%-CI), p-value
NSAIDs only (N = 76)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.5 ± 0.9	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.055 (-0.07; -0.04), p < 0.001	-0.006 (-0.022; 0.011), p = 0.49
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.3 ± 1.1	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.07; -0.04), p < 0.001	-0.005 (-0.023; 0.13), p = 0.58
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	2.9 ± 1.1	-0.03 (-0.035; -0.025), p < 0.001	-0.03 (-0.037; -0.021), p < 0.001	-0.03 (-0.045; -0.02), p < 0.001	-0.003 (-0.02; 0.13), p = 0.67

BISS	56.6 ± 19.2	56.2 ± 20.1	54.4 ± 19.8	-0.87 (-0.96; -0.78), p < 0.001	-0.87 (-1.01; -0.73), p < 0.001	-0.86 (-1.09; -0.63), p < 0.001	0.003 (-0.29; 0.29), p = 0.98
Paracetamol only (N=62)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.03), p < 0.001	0.006 (-0.012; 0.24), p = 0.49
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.3 ± 1.1	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.04 (-0.06; -0.02), p < 0.001	0.009 (-0.01; 0.28), p = 0.36
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.2 ± 1.1	-0.03 (-0.035; -0.025), p < 0.001	-0.03 (-0.037; -0.021), p < 0.001	-0.035 (-0.048; -0.021), p < 0.001	-0.005 (-0.022; 0.12), p = 0.59
BISS	56.6 ± 19.2	56.2 ± 20.1	57.5 ± 15.3	-0.87 (-0.96; -0.78), p < 0.001	-0.87 (-1.01; -0.73), p < 0.001	-0.74 (-0.99; -0.48), p < 0.001	0.16 (-0.14; 0.47), p = 0.30
NSAIDs and paracetamol (N = 39)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.03), p < 0.001	0.0003 (-0.02; 0.02), p = 0.97
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.6 ± 0.9	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.06; -0.04), p < 0.001	-0.05 (-0.07; -0.03), p < 0.001	-0.003 (-0.025; 0.018), p = 0.75
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.2 ± 1.1	-0.03 (-0.035; -0.025), p < 0.001	-0.03 (-0.037; -0.021), p < 0.001	-0.03 (-0.048; -0.018), p < 0.001	-0.006 (-0.026; 0.014), p = 0.56
BISS	56.6 ± 19.2	56.2 ± 20.1	63.2 ± 14.4	-0.87 (-0.96; -0.78), p < 0.001	-0.87 (-1.00; -0.73), p < 0.001	-0.96 (-1.24; -0.68), p < 0.001	-0.11 (-0.46; 0.24), p = 0.54