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RESEARCH ARTICLE

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

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Background: Many mood disorder patients need analgesics due to increased pain sensitivity. Recent studies have suggested that nonsteroidal 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, body mass index, 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 nonusers with respect to treatment outcome with lithium or quetiapine at any time point during 6 months treatment on the overall CGI-BP ($\beta = 0.001$ (95% CI = −0.01 to −0.01), $P = .87$), the BISS ($\beta = 0.01$ (95% CI = −0.17 to 0.15), $P = .91$), 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 nonusers (all $P > .3$).

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.

KEYWORDS
bipolar disorder, nonsteroidal anti-inflammatory drugs (NSAIDs), lithium, polypharmacy, paracetamol, quetiapine

1 | INTRODUCTION

Treatment outcomes in affective disorders, that is unipolar and bipolar depression, are often suboptimal (Nierenberg, 2013). This is further complicated by the presence of comorbid occurring somatic diseases (e.g., painful states), which have been associated with worse treatment effects (Iosifescu, Bankier, & Fava, 2004; Sylvia et al., 2015). 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 nonsteroidal anti-inflammatory drugs (NSAIDs) may worsen the outcomes of selective serotonin reuptake inhibitor (SSRI) treatment (Gallagher et al., 2012; Warner-Schmidt, Vanover, Chen, Marshall, & Greengard, 2011). However, these findings are controversial (Shelton, 2012), and since NSAIDs are frequently used among individuals taking SSRIs (Kohler, Petersen, Mors, & Gasse, 2015), 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 (Uher et al., 2012). 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 (Kohler et al., 2015) or lithium (Stolk et al., 2010). Other studies have actually indicated that short-term, adjunctive NSAID treatment may yield additional antidepressant treatment effects (Kohler et al., 2014; Nery et al., 2008). Finally, it has been suggested that the findings associating NSAIDs with poorer antidepressant treatment response may be explained by confounding factors, for example, residual confounding (Gallagher et al., 2012; Shelton, 2012), 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 above-mentioned 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.

Abbreviations: BISS, Bipolar Inventory of Symptoms Scale; BMI, body mass index; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; GENDEP, Genome-Based Therapeutics Drugs for Depression; NSAIDs, nonsteroidal anti-inflammatory drugs; ORs, odds ratios; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; WBC, white blood cell count

2 | MATERIALS AND METHODS

2.1 | Setting

The present study represents a secondary analysis from the Bipolar CHOICE study (Nierenberg et al., 2014). Bipolar CHOICE was a 6-month multisite, 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 (Nierenberg et al., 2014).

2.2 | 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) $\geq$3 (Spearing, Post, Leverich, Brandt, & Nolen, 1997)) 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 (Sheehan et al., 1998). Psychiatric symptom severity was measured with the CGI-BP (Spearing et al., 1997) and the Bipolar Inventory of Symptoms Scale (BISS) (Bowden et al., 2007; Gonzalez et al., 2008). 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., eight follow-up visits). Clinical interviews obtained demographic information and medical history.

2.3 | NSAID and paracetamol use

At baseline and the eight follow-up visits, the medication doses and dose changes were captured on the Medication Recommendation Tracking Form (Reilly-Harrington et al., 2013). In agreement with prior studies (Gallagher et al., 2012; Uher et al., 2012; Warner-Schmidt et al., 2011), 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 that 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 (Gallagher et al., 2012; Uher et al., 2012; Warner-Schmidt et al., 2011). 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.

2.4 | Statistical analysis

We included baseline information on the following covariates that 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 nonusers and report β-coefficients including 95% CI. These models allow inclusion of all relevant covariates across repeated measurements and efficiently handle missing data (Lane, 2008). We compared users of NSAIDs/paracetamol with nonusers 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 nine assessments (i.e., baseline and eight 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 nonusers 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 nonusers. 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.

2.5 | Sensitivity analyses

First, we performed age- and gender-specific analyses. Second, 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 $\geq 10 \times 10^9$/L (i.e., leukocytosis), indicates an inflammatory response. We investigated whether NSAID/paracetamol use changed treatment outcome among individuals with a baseline WBC $\geq 10 \times 10^9$/L, respectively, among individuals with a baseline WBC $< 10 \times 10^9$/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 nonusers with missing data concerning comedication at ≥1 study visits (N = 105 (34.4%) of the 305 nonusers), and we investigated whether the exclusion of the nonusers with missing data affected our results.

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

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

382 patients completed all nine 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 to −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 to −0.044), whereas nonusers decreased by a β of −0.051 per week (95% CI = −0.058 to −0.044). All results were significant ($P < .001$). When comparing users of NSAIDs or paracetamol to nonusers regarding the decrease in overall CGI-BP, we found no difference as indicated by a β of −0.001 (95% CI = −0.01 to 0.01), $P = .87$). Furthermore, we found no differences between users and nonusers on the BISS (β = 0.01, 95% CI = −0.17; 0.15, $P = .91$) nor on the CGI-BP subscales for depression ($P = .86$) or mania ($P = .51$). In addition, we found no significant differences between NSAID/paracetamol users and nonusers at any time point during the 6-month follow-up (Fig. 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 nonusers, we found that there was not a

TABLE 1 Baseline information for 482 patients with bipolar disorder, divided into nonusers[a] and users[a] of NSAIDs or paracetamol

	Total	Nonusers of NSAIDs or paracetamol[a]	Users of NSAIDs or paracetamol[a]	Users vs. nonusers[b] 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 (sub-threshold)	75 (15.6)	49 (16.1)	26 (14.7)	0.90 (0.53–1.50)

NSAID, nonsteroidal anti-inflammatory drug.

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

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

Bold values represent significant results.

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 $P > .05$ as shown in Table 3). During 6 months of treatment with lithium, respectively, quetiapine, we found no significant differences between NSAID/paracetamol users and nonusers at any time point on the CGI-BP or on the BISS (Fig. 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 ($P = .53$) and the BISS ($P = .42$). The unadjusted models showed very similar results (results not shown).

TABLE 2 Effect of additional use[a] of NSAIDs or paracetamol versus nonusers[a] during 24 weeks of mood-stabilizing treatment: results of mixed effects linear regression analyses[b]

	Baseline			Estimated change per week			Estimated difference
	Total	Nonusers[a]	Users[a]	Total	Nonusers[a]	Users[a]	Users[a] vs. nonusers[a]
	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 to −0.04), *P* < .001	−0.051 (−0.058 to −0.044), *P* < .001	−0.052 (−0.060 to −0.044), *P* < .001	−0.001 (−0.01 to 0.01), *P* = .87
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.4 ± 1.1	−0.05 (−0.06 to −0.04), *P* < .001	−0.049 (−0.056 to −0.042), *P* < .001	−0.05 (−0.059 to −0.041), *P* < .001	−0.001 (−0.012 to 0.01), *P* = .86
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.1 ± 1.1	−0.03 (−0.035 to −0.025), *P* < .001	−0.029 (−0.035 to −0.022), *P* < .001	−0.032 (−0.039 to −0.025), *P* < .001	−0.003 (−0.013 to 0.006), *P* = .51
BISS	56.6 ± 19.2	56.2 ± 20.1	57.4 ± 17.4	−0.87 (−0.96 to −0.78), *P* < .001	−0.88 (−0.99 to −0.77), *P* < .001	−0.87 (−1.00 to −0.73), *P* < .001	0.01 (−0.17 to 0.15), *P* = .91

β, regression coefficient; 95% CI, 95% confidence interval; SD, standard deviation; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; NSAID, nonsteroidal 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 nonusers.

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

[b]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.

3.2 | 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 nonusers of NSAIDs or paracetamol, we found no significant difference in 6 months 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 $P > .05$, results not shown).

3.3 | Sensitivity analyses

We found no differences in age-specific or gender separate analyses (all $P > .05$, 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 $\geq 10 \times 10^9$/L, indicating an inflammatory response, or among 432 individuals with a baseline WBC $< 10 \times 10^9$/L (all $P > .05$, results not shown). Furthermore, of the 240 individuals randomized to lithium, 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 nonusers of NSAIDs/paracetamol with no differences at any time point during the 6-month study period (all $P > .05$, results not shown). Finally, we found no significant differences between NSAID/paracetamol users and nonusers after exclusion of the 105 nonusers with missing data regarding comedication (all $P > .05$, results not shown).

4 | DISCUSSION

NSAIDs and paracetamol are among the most frequently used drugs among individuals with affective disorders due to somatic comorbidity and increased pain sensitivity (Kohler et al., 2015). 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 (Gallagher et al., 2012; Uher et al., 2012; Warner-Schmidt et al., 2011). Within the Bipolar CHOICE trial including 482 patients with bipolar disorder, use of NSAIDs and paracetamol, compared to nonuse, 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

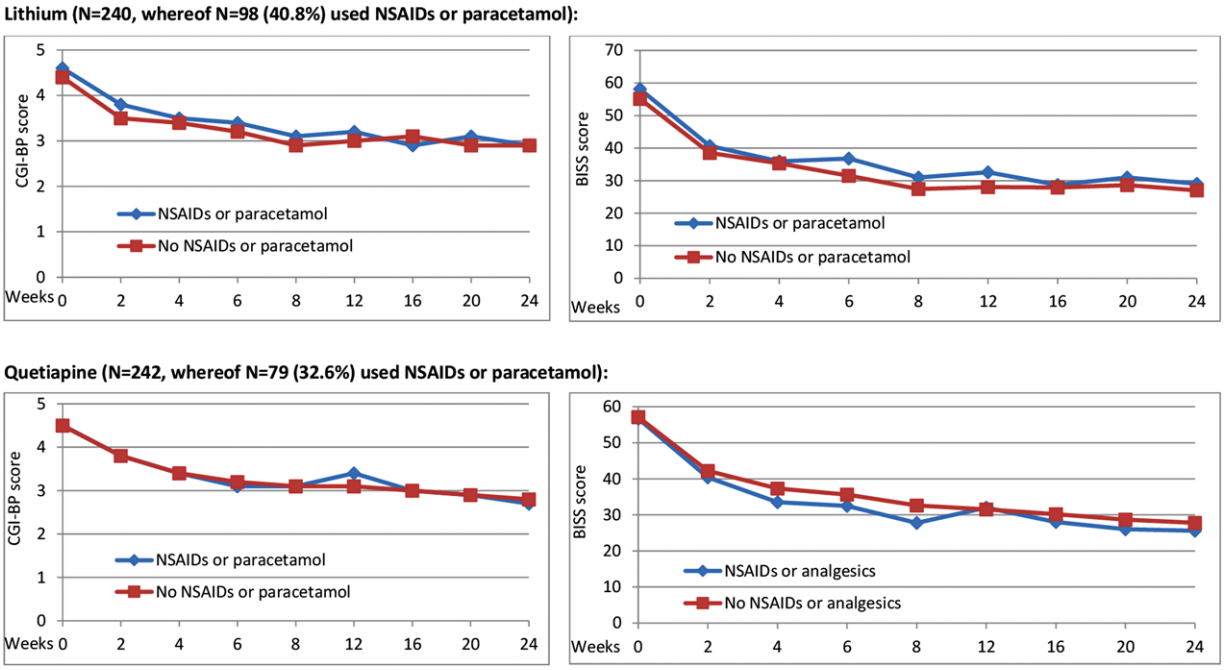

FIGURE 1 CGI-BP and BISS scores during 6 months of follow-up* among 240 individuals randomized to lithium (top two figures), respectively, 242 individuals randomized to quetiapine (bottom two figures).
There were no significant differences between users of NSAIDs/paracetamol and nonusers at any time point (all $P > .05$). CGI-BP, clinical global impression for bipolar disorder; BISS, bipolar inventory symptom scale; NSAID, nonsteroidal 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 3 Effect of additional use[a] of NSAIDs or paracetamol versus nonusers[a] during 24 weeks of treatment among individuals randomized to lithium or quetiapine: results of mixed effects linear regression analyses[b]

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

β, regression coefficient; 95% C, 95% confidence Interval; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; NSAID, nonsteroidal 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 nonusers.
[a]Users are individuals who used NSAIDs or paracetamol at significant dosages at ≥1 visit during the follow-up period.
[b]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.

possible outcomes, adjusted for important covariates, and conducted several subanalyses. Hence, our results support findings (Stolk et al., 2010; Uher et al., 2012) 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.

4.1 | 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 (Gallagher et al., 2012; Warner-Schmidt et al., 2011). The results associated NSAIDs with worse outcomes of SSRI treatment, and the authors concluded that "clinicians should carefully balance the therapeutic benefits of anti-inflammatory agents versus the potentially negative consequences of antagonizing the therapeutic efficacy of antidepressant agents in patients suffering from depression" (Warner-Schmidt et al., 2011). 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

TABLE 4 Effect of additional use[a] of NSAIDs only, paracetamol only, or the combination versus nonusers[a] during 24 weeks of mood-stabilizing treatment: results of mixed effects linear regression analyses[b]

	Baseline			Estimated change per week			Estimated difference
	Total	Nonusers[a]	Users[a]	Total	Nonusers[a]	Users[a]	Users[a] vs. nonusers[a]
	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 to -0.04), $P < .001$	−0.05 (−0.06 to −0.04), $P < .001$	−0.055 (−0.07 to −0.04), $P < .001$	−0.006 (−0.022 to 0.011), $P = .49$
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.3 ± 1.1	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.07 to −0.04), $P < .001$	−0.005 (−0.023 to 0.13), $P = .58$
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	2.9 ± 1.1	−0.03 (−0.035 to −0.025), $P < .001$	−0.03 (−0.037 to −0.021), $P < .001$	−0.03 (−0.045 to −0.02), $P < .001$	−0.003 (−0.02 to 0.13), $P = .67$
BISS	56.6 ± 19.2	56.2 ± 20.1	54.4 ± 19.8	−0.87 (−0.96 to −0.78), $P < .001$	−0.87 (−1.01 to −0.73), $P < .001$	−0.86 (−1.09 to −0.63), $P < .001$	0.003 (−0.29 to 0.29), $P = .98$
Paracetamol only ($N = 62$)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.03), $P < .001$	0.006 (−0.012 to 0.24), $P = .49$
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.3 ± 1.1	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.04), $P < .001$	−0.04 (−0.06 to −0.02), $P < .001$	0.009 (−0.01 to 0.28), $P = .36$
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.2 ± 1.1	−0.03 (−0.035 to −0.025), $P < .001$	−0.03 (−0.037 to −0.021), $P < .001$	−0.035 (−0.048 to −0.021), $P < .001$	−0.005 (−0.022 to 0.12), $P = .59$
BISS	56.6 ± 19.2	56.2 ± 20.1	57.5 ± 15.3	−0.87 (−0.96 to −0.78), $P < .001$	−0.87 (−1.01 to −0.73), $P < .001$	−0.74 (−0.99 to −0.48), $P < .001$	0.16 (−0.14 to 0.47), $P = .30$
NSAIDs and paracetamol ($N = 39$)							
CGI-BP overall	4.5 ± 0.9	4.5 ± 0.9	4.6 ± 0.8	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.03), $P < .001$	0.0003 (−0.02 to 0.02), $P = .97$
CGI-BP depression	4.2 ± 1.1	4.2 ± 1.2	4.6 ± 0.9	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.06 to −0.04), $P < .001$	−0.05 (−0.07 to −0.03), $P < .001$	−0.003 (−0.025 to 0.018), $P = .75$
CGI-BP mania	3.0 ± 1.3	3.0 ± 1.3	3.2 ± 1.1	−0.03 (−0.035 to −0.025), $P < .001$	−0.03 (−0.037 to −0.021), $P < .001$	−0.03 (−0.048 to −0.018), $P < .001$	−0.006 (−0.026 to 0.014), $P = .56$
BISS	56.6 ± 19.2	56.2 ± 20.1	63.2 ± 14.4	−0.87 (−0.96 to −0.78), $P < .001$	−0.87 (−1.00 to −0.73), $P < .001$	−0.96 (−1.24 to −0.68), $P < .001$	−0.11 (−0.46 to 0.24), $P = .54$

β, regression coefficient; 95% CI, 95% confidence interval; SD, standard deviation; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; NSAID, nonsteroidal 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 nonusers.

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

[b] 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.

associated with different treatment effects among 811 patients with depression (Uher et al., 2012). The authors found no differences in treatment outcome among individuals randomized to 12 weeks treatment with the SSRI escitalopram or the TCA nortriptyline. Furthermore, a pharmacoepidemiological study found that NSAID use during lithium treatment was not associated with clinical deterioration (Stolk et al., 2010). Finally, Gallagher et al. 2012 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. This cautiousness has also been emphasized by other researchers (Shelton, 2012).

Other studies have actually indicated that targeted short-term NSAID treatment may improve the treatment outcomes when used as add-on to antidepressants (Muller et al., 2006) or mood stabilizers (Nery et al., 2008). Indeed, it has been discussed that specific subgroups of patients with affective disorders, for example, those with increased pro-inflammatory biomarkers, may benefit of additional NSAID treatment (Kohler et al., 2014; Raison et al., 2013; Rapaport et al., 2016).

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 (Uher et al., 2012) suggesting that NSAIDs and paracetamol do not negatively impact the treatment of affective disorders. Nevertheless, NSAIDs have been associated with side effects, such as an increased risk for gastrointestinal bleeding (De Abajo & Garcia-Rodriguez, 2008) and cardiovascular events (Schjerning Olsen et al., 2011). Hence, clinicians should always balance the beneficial pain-relieving effects of NSAIDs and paracetamol against the risk for side effects for each patient individually.

4.2 | 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 (Reilly-Harrington et al., 2013), minimizing the risk for missing the use of these compounds, that is, 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 (Gallagher et al., 2012; Warner-Schmidt et al., 2011; Uher et al., 2012) 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 that does reduce the generalizability of these data despite our efforts to mimic real-world patients by having very few inclusion and exclusion criteria.

4.3 | Conclusion

Among 482 participants from the Bipolar CHOICE study, 177 (37%) used NSAIDs and/or paracetamol at therapeutic doses during 6 months 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 months 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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CONFLICT 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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Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Schering-Plough, and Solvay/Wyeth.

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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).

Dr. Bowden currently has no activities or consultant relationships to disclose.

Dr. McInnis has received grants for research support from NIMH, the Heinz C. Prechter Research Fund, and the Michigan Institute for Clinical Health Research (MICHR). He has received consulting income from the Qatar National Research Foundation and Merck Pharmaceuticals.

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Dr. Friedman receives royalties from Springer. He has served as an expert forensic consultant for Thomson Rhodes & Cowie P.C. and Berger and Zavesky Co. L.P.A. Dr. Friedman received grant support from NIMH, AHRQ, Novartis, St. Jude Medical, Medtronics, Repligen, AstraZeneca, Roche, and Takeda and Neosync.

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.

Dr. Shelton has served as a consultant to Acadia Pharmaceuticals, Bristol-Myers Squibb, Cyberonics, Inc., Elan, Corp., Euthymics Bioscience, Cerecor Inc., Clintara LLC, Forest Pharmaceuticals, Janssen Pharmaceutica, Medtronic, Inc., MSI Methylation Sciences, Naurex, Inc., Nestle' Health Science - Pamlab, Inc., Otsuka Pharmaceuticals, Pfizer, Inc., Ridge Diagnostics, Shire PLC, and Takeda Pharmaceuticals. Dr. Shelton has received research grant support from Appian Labs, Elan, Corp., Euthymics Bioscience, Forest Pharmaceuticals, Janssen Pharmaceutica, Naurex, Inc, Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Nestle' Health Science - Pamlab, Inc., Repligen, Corp., Ridge Diagnostics, and Takeda Pharmaceuticals.

Andrew A. Nierenberg is a consultant for the Abbott Laboratories, Alkermes, American Psychiatric Association, Appliance Computing Inc. (Mindsite), Basliea, Brain Cells, Inc., Brandeis University, Bristol Myers Squibb, Clintara, Corcept, Dey Pharmaceuticals, Dainippon Sumitomo (now Sunovion), Eli Lilly and Company, EpiQ, L.P./Mylan Inc., Forest, Genaissance, Genentech, GlaxoSmithKline, Hoffman LaRoche, Infomedic, Intra-Cellular Therapies, Lundbeck, Janssen Pharmaceutica, Jazz Pharmaceuticals, Medavante, Merck, Methylation Sciences, Naurex, NeuroRx, Novartis, Otsuka, PamLabs, Parexel, Pfizer, PGx Health, Ridge Diagnostics Shire, Schering-Plough, Somerset, Sunovion, Takeda Pharmaceuticals, Targacept, and Teva; consulted through the MGH Clinical Trials Network and Institute (CTNI) for Astra Zeneca, Brain Cells, Inc., Dianippon Sumitomo/Sepracor, Johnson and Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept, and Takeda/Lundbeck Pharmaceuticals. He receives grant/research support from American Foundation for Suicide Prevention, AHRQ, Brain and Behavior Research Foundation, Bristol-Myers Squibb, Cederroth, Cephalon, Cyberonics, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen Pharmaceutica, Intra-Cellular Therapies, Lichtwer Pharma, Marriott Foundation, Mylan, NIMH, PamLabs, PCORI, Pfizer Pharmaceuticals, Shire, Stanley Foundation, Takeda, and Wyeth-Ayerst. Honoraria include Belvoir Publishing, University of Texas Southwestern Dallas, Brandeis University, Bristol-Myers Squibb, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Baystate Medical Center, Columbia University, CRICO, Dartmouth Medical School, Health New England, Harold Grinspoon Charitable Foundation, IMEDEX, Israel Society for Biological Psychiatry, Johns Hopkins University, MJ Consulting, New York State, Medscape, MBL Publishing, MGH Psychiatry Academy, National Association of Continuing Education, Physicians Postgraduate Press, SUNY Buffalo, University of Wisconsin, University of Pisa, University of Michigan, University of Miami, University of Wisconsin at Madison, World Congress of Brain Behavior and Emotion, APSARD, ISBD, SciMed, Slack Publishing and Wolters Klower Publishing ASCP,

NCDEU, Rush Medical College, Yale University School of Medicine, NNDC, Nova Southeastern University, NAMI, Institute of Medicine, CME Institute, and ISCTM. He was currently or formerly on the advisory boards of Appliance Computing, Inc., Brain Cells, Inc., Eli Lilly and Company, Genentech, Johnson and Johnson, Takeda/Lundbeck, Targacept, and InfoMedic. He owns stock options in Appliance Computing, Inc., Brain Cells, Inc., and Medavante; has copyrights to the Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH Clinical Trials Network and Institute (CTNI).

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