Original Investigation | META-ANALYSIS

Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects
A Systematic Review and Meta-analysis of Randomized Clinical Trials

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IMPORTANCE Several studies have reported antidepressant effects of anti-inflammatory treatment; however, the results have been conflicting and detrimental adverse effects may contraindicate the use of anti-inflammatory agents.

OBJECTIVE To systematically review the antidepressant and possible adverse effects of anti-inflammatory interventions.

DATA SOURCES Trials published prior to December, 31, 2013, were identified searching Cochrane Central Register of Controlled Trials, PubMed, EMBASE, PsychINFO, Clinicaltrials.gov, and relevant review articles.

STUDY SELECTION Randomized placebo-controlled trials assessing the efficacy and adverse effects of pharmacologic anti-inflammatory treatment in adults with depressive symptoms, including those who fulfilled the criteria for depression.

DATA EXTRACTION AND SYNTHESIS Data were extracted by 2 independent reviewers. Pooled standard mean difference (SMD) and odds ratios (ORs) were calculated.

MAIN OUTCOMES AND MEASURES Depression scores after treatment and adverse effects.

RESULTS Ten publications reporting on 14 trials (6262 participants) were included: 10 trials evaluated the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 4258) and 4 investigated cytokine inhibitors (n = 2004). The pooled effect estimate suggested that anti-inflammatory treatment reduced depressive symptoms (SMD, −0.34; 95% CI, −0.57 to −0.11; I^2 = 90%) compared with placebo. This effect was observed in studies including patients with depression (SMD, −0.54; 95% CI, −1.08 to −0.01; I^2 = 68%) and depressive symptoms (SMD, −0.27; 95% CI, −0.53 to −0.01; I^2 = 68%). The heterogeneity of the studies was not explained by differences in inclusion of clinical depression vs depressive symptoms or use of NSAIDs vs cytokine inhibitors. Subanalyses emphasized the antidepressant properties of the selective cyclooxygenase 2 inhibitor celecoxib (SMD, −0.29; 95% CI, −0.49 to −0.08; I^2 = 73%) on remission (OR, 7.89; 95% CI, 2.94 to 21.17; I^2 = 0%) and response (OR, 6.59; 95% CI, 2.24 to 19.42; I^2 = 0%). Among the 6 studies reporting on adverse effects, we found no evidence of an increased number of gastrointestinal or cardiovascular events after 6 weeks or infections after 12 weeks of anti-inflammatory treatment compared with placebo. All trials were associated with a high risk of bias owing to potentially compromised internal validity.

CONCLUSIONS AND RELEVANCE Our analysis suggests that anti-inflammatory treatment, in particular celecoxib, decreases depressive symptoms without increased risks of adverse effects. However, a high risk of bias and high heterogeneity made the mean estimate uncertain. This study supports a proof-of-concept concerning the use of anti-inflammatory treatment in depression. Identification of subgroups that could benefit from such treatment might be warranted.

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Compelling evidence suggests that subgroups of major depressive disorder may be associated with an inflammatory state.[1] Findings include elevated levels of cytokines[2,3] and an increased susceptibility for autoimmune diseases and infections.[4] Furthermore, treatment with proinflammatory agents induces symptoms of depression.[5]

Thus, studies have investigated whether the use of anti-inflammatory agents could improve the antidepressant response. Nonsteroidal anti-inflammatory drugs (NSAIDs), in particular the selective cyclooxygenase 2 (COX-2) inhibitor celecoxib,[6] and cytokine inhibitors[7] have shown promising results in clinical trials. Nonsteroidal anti-inflammatory drugs and cytokine inhibitors exert anti-inflammatory effects by inhibiting proinflammatory cytokines. Cytokine inhibitors act directly on these cytokines,[7] whereas NSAIDs inhibit the enzyme COX-2,[6] which is responsible for cytokine production. However, sample sizes in most clinical trials were small and the results were conflicting, particularly in NSAID studies; observational trials[8,9] have associated NSAIDs with worse antidepressant treatment effects. Several adverse effects associated with anti-inflammatory treatment have been well described[10-12] and should be considered in the evaluation of benefits and risks.

Nevertheless, the observed significant effects in small study groups support the evidence of potential antidepressant effects of anti-inflammatory treatment. Two recent meta-analyses have associated celecoxib add-on treatment[13] and NSAID monotherapy[14] with antidepressant effects. However, these meta-analyses[13,14] did not include an assessment of potential bias for the included studies, making an overall assessment based solely on pooling of effect sizes problematic. It is important to evaluate the overall effect of anti-inflammatory intervention, including a broader range of studies, and compare a potential antidepressant effect with the risk for adverse effects. Trials with unclear or inadequate methodologic quality may be associated with risk of bias (systematic error) compared with trials using adequate methods, possibly leading to overestimation of intervention benefits and underestimation of harms.[15] In addition, the width of clinical findings indicates the importance of not only investigating the effect of anti-inflammatory agents on depression[13] or depressive symptoms[14] and one compound[13,14] but also including the entire spectrum of individuals with depressive symptoms and the entire range of anti-inflammatory agents.

The objectives of this systematic review and meta-analysis were to investigate the antidepressant effect of anti-inflammatory treatment and to assess possible adverse effects of these interventions in adults with depressive symptoms or depression. Investigations of the concomitant use of antidepressants and anti-inflammatory agents are of major public concern because anti-inflammatory agents, in particular NSAIDs, are frequently used by individuals receiving antidepressants, probably owing to the bidirectional relationship between depression and pain.[16]

Methods

The current meta-analysis aimed to include all evidence from clinical trials that have investigated anti-inflammatory treatment in depression, regardless of whether the anti-inflammatory treatment was used alone or as add-on therapy. We were interested in both antidepressant treatment effects and adverse events among adults.

Eligibility Criteria

Only randomized clinical trials were included in the meta-analysis (ie, the allocation of participants to intervention and comparison groups was described as *randomized*). We assessed studies investigating patients of both sexes older than 17 years. Patients could have either a diagnosis of depression or experience depressive symptoms that did not meet the criteria for depression. Because we were interested in the effect of anti-inflammatory treatment on depressive symptoms in general, trials were included regardless of concomitant disease among the patients or whether the trials included the measurement of depressive symptoms in otherwise healthy individuals. Depression was diagnosed according to a diagnostic system (Research Diagnostic Criteria, *International Classification of Diseases*, or *DSM-IV*). Depressive symptoms were rated with clinician-rated scales or self-report questionnaires (eg, Patient Health Questionnaire-9 and Hospital Anxiety and Depression Scale-Depression). The trials had to allocate participants to (1) an anti-inflammatory drug or a control group (eg, placebo or treatment as usual) or (2) an anti-inflammatory drug as add-on treatment (eg, a selective serotonin reuptake inhibitor [SSRI] with an anti-inflammatory drug vs an SSRI with a placebo). We defined *anti-inflammatory treatment* as NSAIDs, COX-2 inhibitors, proinflammatory cytokine inhibitors, and minocycline hydrochloride.

Search Methods for Identification of Trials

We searched Cochrane Central Register of Controlled Trials, PubMed, EMBASE, PsychINFO, and the National Institutes of Health website Clinicaltrials.gov for studies published before December 31, 2013, using the following Medical Subject Headings (or similar headings) or text word terms: *major depressive disorder*, *depression* or *depressive symptoms* in combination with *anti-inflammatory*, *anti-inflammatory agent*, *non-steroidal anti-inflammatory*, *NSAID*, *acetylsalicylic acid, cyclooxygenase 2 inhibitor*, *COX-2*, *antibiotics*, *celecoxib*, *infliximab*, *etanercept*, or *minocycline*. Reference lists of relevant reviews were searched for additional trials. One investigator (O.K.) examined titles and abstracts to remove obviously irrelevant reports. Two investigators (O.K. and J.K.) examined the remaining full-text reports to determine the study's compliance with inclusion criteria.

Data Extraction

Data were extracted independently (O.K., with assistance from J.K.) using a pre-piloted structured form. The extractors were not blinded to the study results, authors, or institutions. In addition to bibliographic information, data extraction included quality assessment, description of the participants, description of the intervention and control groups, psychometric data, and outcomes. We contacted authors of the articles identified by e-mail to learn details missing from the Methods and Results sections of the reports and deter-

mine the authors' knowledge of or involvement in any current work in the area.

Outcome Measures

Primary outcome measures included (1) a significant reduction in depressive symptoms measured on a continuous scale at the end of an intervention, (2) response (ie, a binary outcome of the proportion of participants in each intervention group who were defined as having responded to treatment [50% reduction in depression severity]) measured at the end of the intervention, (3) serious adverse effects including gastrointestinal and cardiovascular events for NSAIDs and infections for all other drugs, and (4) remission in patients with depression (ie, a binary outcome of the proportion of participants in each intervention group whose condition was classified, for example, as a Hamilton Scale for Depression score <7 at the end of an intervention). Some trials had several intervention groups, which we analyzed by pooling data from the experimental groups and comparing them with data from the control group. Secondary outcome measures included (1) nonserious adverse effects, (2) depressive symptoms measured on a continuous scale at maximal follow-up, and (3) remission at maximal follow-up.

Assessment of Bias

The bias risks of the randomized clinical trials included were assessed (J.K.). Based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*[17] and methodologic studies,[18-21] we extracted data regarding quality for 5 domains. Sequence generation was considered adequate if the authors described a random component. Allocation concealment was adequate if it was justified that neither participants nor investigators could foresee the assignment. Blinding of outcome assessors was adequate if the trial was characterized as double-blind; however, blinding of outcome assessors was not inferred from the term *double-blind*, and in cases in which the outcome was self-reported, participants were considered outcome assessors. Analyses were considered intention to treat if missing data were handled by adequate methods (mixed models, multiple imputations, or similar methods) or if no missing data were observed. For-profit bias was considered low if the trial appeared to be free of industry sponsorship or any other kind of for-profit support.

Trials were assessed as having a low risk of bias if the review of all of the individual domains was considered to show a low risk of bias. Trials assessed as having uncertain risk of bias or high risk of bias in one or more of the individual domains were considered trials with a high risk of bias.

Statistical Analysis

We estimated a standardized mean difference (SMD) for each study using the Cohen *d* test. The SMD is the mean difference in the depression score between the intervention and control groups divided by the pooled SD of the distribution of the score used in the study. The result is a unitless effect-size measure readily comparable to other studies using similar measures of outcome. By convention, effect sizes of 0.2, 0.4, and 0.8 are considered small, medium, and large, respectively. For dichotomous variables, we calculated the relative risks with 95% CIs. We decided a priori to use a random-effects analysis because of expected heterogeneity due to different treatment regimens and patient populations. In addition, we calculated the pooled odds ratio (OR) for response and remission in the included trials.

The χ^2 test for heterogeneity provided an indication of between-trial heterogeneity. In addition, the degree of heterogeneity observed in the results was quantified using the I^2 statistic,[22] which can be interpreted as the percentage of variation observed between the trials attributable to between-trial differences rather than sampling error (chance). We used RevMan, version 5.2, for calculations.[23]

Subgroup Analysis

We decided a priori to perform subanalyses of both depression and depressive symptoms and of the selective COX-2 inhibitor celecoxib. Subgroup differences were tested using RevMan, version 5.2. This method is based on fixed-effects analysis using the inverse variance method.

Discrepancies From the Protocol

We decided to include response as an outcome. We were not able to analyze the effect of baseline cytokine levels, since only 1 trial reported baseline C-reactive protein (CRP) levels[24] and 1 trial reported baseline interleukin 6 (IL-6) levels.[25]

Results

Search Results and Study Characteristics

Using our search criteria, 1500 records were identified, of which 53 were assessed for abstract and full-text inspection (eFigure 1 in the Supplement). We included 10 publications comprising 14 randomized clinical trials investigating the antidepressant effects of anti-inflammatory treatment in 6262 adults.

Ten trials investigated NSAIDs, 4 as add-on treatment,[6,25-27] and 6 as monotherapy (**Table 1**).[14,28] Four trials studied cytokine inhibitors, all as monotherapy.[7,24,29,30] Depression was investigated by 5 studies and depressive symptoms by 9 studies. Nine trials included patients with somatic comorbidity, such as active osteoarthritis or psoriasis; 1 trial[28] evaluated healthy individuals with a family history of Alzheimer-like dementia (Table 1). Length of treatment ranged between 6 and 12 weeks; only 1 study[28] examined NSAID monotherapy during a 12-month period.

Treatment Effect of Anti-inflammatory Intervention: Primary Outcomes

For the study by Tyring et al,[7] we had information only for performing analyses on response (50% reduction in depression severity) and adverse effects. In 11 of the 13 available trials, anti-inflammatory treatment was found to yield antidepressant effects with a pooled effect estimate of −0.34 (95% CI, −0.57 to −0.11; $P = .004$) (**Figure 1**). However, this effect estimate was associated with high heterogeneity, reflected by $I^2 = 90\%$. The overall result from fixed-effects analysis was −0.20 (95% CI, −0.26 to −0.14; $P < .001$).

Table 1. Baseline Characteristics of Identified Clinical Trials Investigating Anti-inflammatory Treatment in Depression

Source	Type	Patient Population: No. of Patients Randomized	No. of Patients Analyzed	No. (%) of Males/Age, y	Comorbidity	Biochemistry: Baseline	Biochemistry: Posttreatment	Depression Diagnosis	Treatment, No.
NSAIDs									
Müller et al,[6] 2006	Peer reviewed	40	18	20 (50)/23-65	None	Not measured	Not measured	*DSM-IV*, HAM-D_{17}	6 wk of NARI with placebo (20) vs NARI with celecoxib, 400 mg, once daily (20)
Akhondzadeh et al,[26] 2009	Peer reviewed	40	37	15 (38)/24-46	None	Not measured	Not measured	*DSM-IV*, HAM-D_{17} ≥18	6 wk of SSRI with placebo (20) vs SSRI with celecoxib, 200 mg, twice daily (20)
Hashemian et al,[27] 2011	Abstract	40	40	Women only/18-50	None	Not measured	Not measured	HAM-D_{17}, 18-36	8 wk of SSRI with placebo (20) vs SSRI with celecoxib, 100 mg, twice daily (20)
Abbasi et al,[25] 2012	Peer reviewed	40	37	27 (68)/18-50	None	IL-6 (pg /mL): placebo 2.78 (0.72); celecoxib 2.79 (0.76)	IL-6 (pg/mL): placebo 2.56 (0.64); celecoxib 2.16 (0.60)	*DSM-IV*, HAM-D_{17} ≥18	6 wk of SSRI with placebo (20) vs SSRI with celecoxib, 200 mg, twice daily (20)
Fields et al,[28] 2012	Peer reviewed	2311	2233	1368 (59.2)/≥70	Family history of Alzheimer-like dementia	Not measured	Not measured	30-Item GDS	12 mo of placebo (986) vs celecoxib, 200 mg, twice daily (656) vs naproxen, 220 mg, twice daily (669)
Iyengar et al,[14] 2013[a]	Peer reviewed	1787	1696	476 (28.1)/≥40 and <50	Active and symptomatic osteoarthritis	Not measured	Not measured	PHQ-9	6 wk of placebo (359) vs ibuprofen, 800 mg, thrice daily (311) or naproxen, 500 mg, twice daily (401), vs celecoxib, 200 mg, once daily (716)
A3191051	Peer reviewed	322	305	≥40 and <50	Active and symptomatic osteoarthritis	Not measured	Not measured	PHQ-9	6 wk of placebo (67) vs celecoxib, 200 mg, once daily (127) or naproxen, 500 mg, twice daily (128)
A3191052	Peer reviewed	367	353	≥40 and <50	Active and symptomatic osteoarthritis	Not measured	Not measured	PHQ-9	6 wk of placebo (79) vs celecoxib, 200 mg, once daily (144) or naproxen, 500 mg, twice daily (130)
A3191053	Peer reviewed	318	291	≥40 and <50	Active and symptomatic osteoarthritis	Not measured	Not measured	PHQ-9	6 wk of placebo (61) vs celecoxib, 200 mg, once daily (127) or naproxen, 500 mg, twice daily (130)

(continued)

Anti-inflammatory treatment revealed superiority compared with placebo with regard to depression in 5 studies including 192 patients (SMD, −0.54; 95% CI, −1.08 to −0.01; P = .05; I^2 = 68%) and depressive symptoms in 8 studies including 5255 patients (SMD, −0.27; 95% CI, −0.53 to −0.01; P = .05; I^2 = 68%) (Figure 1). No significant subgroup difference between depression and depressive symptoms could be detected (P = .37).

Table 1. Baseline Characteristics of Identified Clinical Trials Investigating Anti-inflammatory Treatment in Depression (continued)

Source	Type	Patient Population						Depression Diagnosis	Treatment, No.
		No. of Patients		No. (%) of Males/Age, y	Comorbidity	Biochemistry			
		Randomized	Analyzed			Baseline	Posttreatment		
A3191062	Peer reviewed	387	377	≥40 and <50	Active and symptomatic osteoarthritis	Not measured	Not measured	PHQ-9	6 wk of placebo (79) vs celecoxib, 200 mg, once daily (153) or ibuprofen, 800 mg, thrice daily (155)
A3191063	Peer reviewed	393	370	≥40 and <50	Active and symptomatic osteoarthritis	Not measured	Not measured	PHQ-9	6 wk of placebo (73) vs celecoxib, 200 mg, once daily (165) or ibuprofen, 800 mg, thrice daily (155)
Cytokine inhibitors									
Tyring et al,[7] 2006	Peer reviewed	618	597	419 (67.8)/≥18	Clinically stable psoriasis	Not measured	Not measured	HAM-D_{17}, BDI	12 wk of placebo (307) vs etanercept, 25 mg, twice daily (311) twice weekly
Menter et al,[29]2010	Peer reviewed	96	96	65 (68)/≥18	None	Not measured	Not measured	ZDS	12 wk of early termination placebo (52) vs adalimumab, 40 mg weekly or every other week (44)
Langley et al,[30]2010	Peer reviewed	1230	1230	840 (68.3)/≥18	Psoriasis	Not measured	Not measured	HADS-D	12 wk of placebo (410) vs ustekinumab, 45 mg (409), vs ustekinumab, 90 mg (411), at 0 and 4 wk
Raison et al,[24] 2012	Peer reviewed	60	60	20 (33)/25-60	None	HS-CRP (mg/L): placebo 5.4 (8.2); infliximab 6.3 (8.9)	Change from reported baseline	HAM-D_{17}	12 wk; 3 infusions at wk 0, 2, and 6 of placebo (30) vs infliximab, 5 mg/kg (30)

Abbreviations: BDI, Beck Depression Inventory; GDS, Geriatric Depression Scale; HADS-D, Hospital Anxiety and Depression Scale–Depression; HAM-D_{17}, 17-item Hamilton Scale for Depression; HS-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; NARI, noradrenaline reuptake inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; PHQ-9, Patient Health Questionnaire–9; SSRI, selective serotonin reuptake inhibitor; ZDS, Zung Self-Rating Depression Scale.

[a] The study was a meta-analysis of 5 trials investigating NSAID monotherapy. The trials (A3191051, A3191052, A3191053, A3191062, and A3191063) are presented individually.

Analysis of 2 main anit-inflammatory treatments associated NSAIDs with a pooled-effect estimate of −0.27 (95% CI, −0.45 to −0.08; P = .004; I^2 = 72% [n = 4258]) and cytokine inhibitors with −0.38 (95% CI, −0.88 to 0.12; P = .14; I^2 = 85% [n = 2004]) (**Figure 2**). No subgroup differences could be detected (P = .67). By visual inspection of the forest plot on NSAIDs in Figure 2, the effect estimate obtained in the trial by Fields et al,[28] the only study on healthy individuals, was markedly different. After excluding this study, the pooled effect estimates remained similar (SMD, −0.37; 95% CI, −0.57 to −0.18; P < .001) but with a smaller heterogeneity (I^2 = 76%).

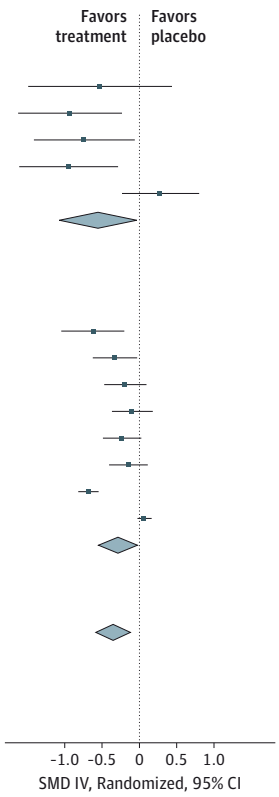
Analyses favored anti-inflammatory treatment over placebo regarding both remission (5 trials [186 patients]; OR, 2.73; 95% CI, 1.37-5.46; P = .004; I^2 = 71%) (eFigure 2 in the Supplement) and response (5 trials [743 patients]; OR, 2.41; 95% CI, 1.12-5.20; P = .02; I^2 = 51%) (eFigure 3 in the Supplement).

Adverse Effects

None of the NSAIDs could be associated with an increased risk for gastrointestinal (3 trials [1770 patients]; OR, 1.04; 95% CI, 0.61-1.79) or cardiovascular (1 trial [1696 patients]; OR, 2.00; 95% CI, 0.25-16.08) adverse effects (**Figure 3**) after 6 weeks of treatment. Specific drugs and dosages are reported in Table 1. Cytokine inhibitors were not significantly associated with infections after 12 weeks of treatment (3 trials [753 patients]; OR, 1.27; 95% CI, 0.89-1.82).

Figure 1. Overall Results of Anti-inflammatory Intervention on Antidepressant Treatment: Depression and Depressive Symptoms

Source	Treatment Mean	Treatment SD	Treatment Total	Placebo Mean	Placebo SD	Placebo Total	SMD IV, Randomized, 95% CI
Depression							
Müller et al,[6] 2006	7.9	7.1	10	12.1	8.3	8	-0.52 (-1.47 to 0.43)
Abbasi et al,[25] 2012	-13.4	3.88	19	-10.05	3.15	18	-0.92 (-1.61 to -0.24)
Akhondzadeh et al,[26] 2009	-13.2	4.26	19	-10.2	3.77	18	-0.73 (-1.40 to -0.06)
Hashemian et al,[27] 2011	12.42	5.0	20	17.33	5.24	20	-0.94 (-1.60 to -0.28)
Raison et al,[24] 2012	-7.6	7.0	30	-9.6	7.0	30	0.28 (-0.23 to 0.79)
Subtotal (95% CI)			**98**			**94**	**-0.54 (-1.08 to -0.01)**
Heterogeneity: τ^2=0.25; χ^2_4 12.64 (P=.01); I^2=68%							
Test for overall effect: z=1.99 (P=.05)							
Depressive symptoms							
Menter et al,[29] 2010	36.2	11.5	44	44.2	14.2	52	-0.61 (-1.02 to -0.20)
A3191053, 2013	4.0	4.652	236	5.62	6.381	55	-0.32 (-0.62 to -0.03)
A3191051, 2013	4.309	4.729	241	5.22	4.939	64	-0.19 (-0.47 to 0.09)
A3191063, 2013	2.578	3.301	304	2.91	3.806	66	-0.10 (-0.36 to 0.17)
A3191052, 2013	2.152	3.523	278	3.03	4.574	75	-0.23 (-0.49 to 0.02)
A3191062, 2013	4.716	4.704	299	5.42	5.688	78	-0.14 (-0.39 to 0.11)
Langley et al,[30] 2010	-1.9	3.26	820	0.21	2.8	410	-0.68 (-0.80 to -0.56)
Fields et al,[28] 2012	3.672	3.643	1283	3.43	3.56	950	0.07 (-0.02 to 0.15)
Subtotal (95% CI)			**3505**			**1750**	**-0.27 (-0.53 to -0.01)**
Heterogeneity: τ^2=0.13; χ^2_7 103.20 (P=.001); I^2=93%							
Test for overall effect: z=2.00 (P=.05)							
Total (95% CI)			**3603**			**1844**	**-0.34 (-0.57 to -0.11)**
Heterogeneity: τ^2=0.13; χ^2_{12} 118.89 (P<.001); I^2=90%							
Test for overall effect: z=2.90 (P=.004)							
Test for subgroup differences: χ^2_1 0.80 (P=.37); I^2=0%							



SMD indicates standard mean difference.

Bias of Included Trials

As reported in **Table 2**, all effects estimated from trial reports were associated with a high risk of bias. Eleven of the 14 trials did not report adequate sequence generation. In each of the categories used (allocation concealment, intention-to-treat analysis, and for-profit bias), most trials were judged to have a high risk of bias. Blinded outcome assessment was the only domain in which all studies showed a low risk of bias.

Subanalyses

All studies investigating NSAIDs included celecoxib. Celecoxib treatment in general could be associated with a trend toward superiority (10 trials [2750 patients]; SMD, −0.29; 95% CI, −0.49 to −0.08; P = .006; I^2 = 73%) (eFigure 4 in the Supplement). After excluding the study by Fields et al,[28] the effect estimate remained similar with decreased heterogeneity: SMD, −0.31 (95% CI, −0.47 to −0.15; I^2 = 32%) (eFigure 5 in the Supplement). When analyzing only the trials on celecoxib monotherapy, the results showed borderline significance (SMD, −0.13; 95% CI, −0.30 to 0.04; I^2 = 66%) (eFigure 4 in the Supplement). Trials using celecoxib as an add-on to antidepressant therapy showed significant improvement compared with placebo (4 trials [132 patients]; SMD, −0.82; 95% CI, −1.17 to −0.46; P < .001), with little heterogeneity (I^2 = 0%) (eFigure 4 in the Supplement). In addition, celecoxib add-on improved both remission (4 trials [132 patients]; OR, 7.89; 95% CI, 2.94 to 21.17; P < .001; I^2 = 0%) (eFigure 6 in the Supplement) and response (3 trials [92 patients]; OR, 6.59; 95% CI, 2.24 to 19.42; P < .001; I^2 = 0%) (eFigure 7 in the Supplement).

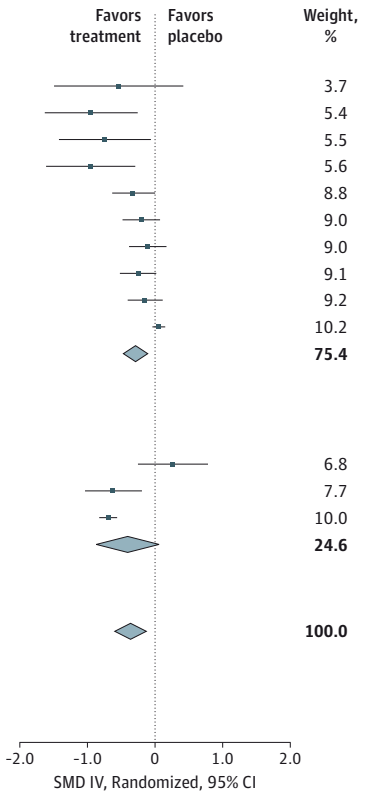
Discussion

To our knowledge, the present meta-analysis is the largest study on anti-inflammatory treatment for depressive symptoms to date, combining data on anti-inflammatory add-on treatment and monotherapy. Fourteen randomized clinical trials with a total of 6262 patients were evaluated. Anti-inflammatory treatment showed a beneficial effect on depressive symptoms. However, this estimate was associated with a high level of heterogeneity. The type of depression, somatic comorbidity, and type of medication or treatment (ie, monotherapy or add-on therapy) did not explain the differences noted in effect estimation. Nonsteroidal anti-inflammatory drugs were associated with a better antidepressant effect in general, with 9 of 10 trials favoring NSAIDs, whereas a statistical trend was observed favoring cytokine inhibitors among 4 studies, but the results remained heterogeneous. Subanalyses of celecoxib showed improved antidepressant effects with little heterogeneity, in particular with add-on treatment.

Our analyses did not associate NSAIDs or cytokine inhibitors with an increased risk for adverse effects. However, not

Figure 2. Overall Results of Anti-inflammatory Intervention on Antidepressant Treatment: Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Cytokine Inhibitors

Source	Treatment Mean	Treatment SD	Treatment Total	Placebo Mean	Placebo SD	Placebo Total	SMD IV, Randomized, 95% CI	Weight, %
NSAIDs								
Müller et al,[6] 2006	7.9	7.1	10	12.1	8.3	8	-0.52 (-1.47 to 0.43)	3.7
Abbasi et al,[25] 2012	-13.4	3.88	19	-10.05	3.15	18	-0.92 (-1.61 to -0.24)	5.4
Akhondzadeh et al,[26] 2009	-13.2	4.26	19	-10.2	3.77	18	-0.73 (-1.40 to -0.06)	5.5
Hashemian et al,[27] 2011	12.42	5.0	20	17.33	5.24	20	-0.94 (-1.60 to -0.28)	5.6
A3191053, 2013	4.0	4.652	236	5.62	6.381	55	-0.32 (-0.62 to -0.03)	8.8
A3191051, 2013	4.309	4.729	241	5.22	4.939	64	-0.19 (-0.47 to 0.09)	9.0
A3191063, 2013	2.578	3.301	304	2.91	3.806	66	-0.10 (-0.36 to 0.17)	9.0
A3191052, 2013	2.152	3.523	278	3.03	4.574	75	-0.23 (-0.49 to 0.02)	9.1
A3191062, 2013	4.716	4.704	299	5.42	5.688	78	-0.14 (-0.39 to 0.11)	9.2
Fields et al,[28] 2012	3.672	3.643	1283	3.43	3.56	950	-0.07 (-0.02 to -0.15)	10.2
Subtotal (95% CI)			**2709**			**1352**	**-0.27 (-0.45 to -0.08)**	**75.4**
Heterogeneity: τ^2=0.05; χ^2_9 32.62 (P<.001); I^2=72%								
Test for overall effect: z=2.85 (P=.004)								
Cytokine inhibitors								
Raison et al,[24] 2012	-7.6	7.0	30	-9.6	7.0	30	0.28 (-0.23 to 0.79)	6.8
Menter et al,[29] 2010	36.2	11.5	44	44.2	14.2	52	-0.61 (-1.02 to -0.20)	7.7
Langley et al,[30] 2010	-1.9	3.26	820	0.21	2.8	410	-0.68 (-0.80 to -0.56)	10.0
Subtotal (95% CI)			**894**			**492**		**24.6**
Heterogeneity: τ^2=0.16; χ^2_2 12.92 (P<.001); I^2=85%								
Test for overall effect: z=1.49 (P=.14)								
Total (95% CI)			**3603**			**1844**	**-0.34 (-0.57 to -0.11)**	**100.0**
Heterogeneity: τ^2=0.13; χ^2_{12} 118.89 (P<.001); I^2=90%								
Test for overall effect: z=2.90 (P=.004)								
Test for subgroup differences: χ^2_1 0.18 (P=.67); I^2=0%								



SMD indicates standard mean difference.

all included studies reported adverse effects, complicating the assessment. Furthermore, most studies were small and most of the observed effect sizes were small to medium with high heterogeneity. In addition, all included trials showed a high risk of bias owing to their potentially compromised internal validity. The bias tended to exaggerate treatment effects, and this could also be the case in the present review.[15] Moreover, the present meta-analysis was restricted to studies with short-term treatment duration, since evaluation of long-term effects was not possible. In addition, the present systematic review included only 14 trials, making detection of publication bias problematic,[31] and we cannot exclude the possibility of unpublished trial results. Finally, the antidepressant effect of NSAIDs may be mediated via their effects on underlying somatic diseases. However, the antidepressant effect of NSAIDs has been shown[14] to be independent of their pain-relieving effect. Hence, our results should be interpreted with caution. Nonetheless, it is possible that specific subgroups would benefit more from anti-inflammatory intervention, such as patients with low-grade inflammation[24] or comorbid inflammatory diseases.[14]

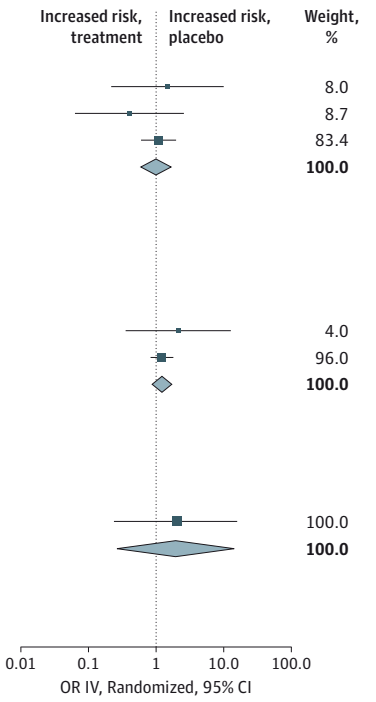
Antidepressant Effects of Anti-inflammatory Agents

Findings on the antidepressant properties of anti-inflammatory intervention have been conflicting. Most randomized studies associated NSAIDs, in particular celecoxib, with antidepressant effects.[6,25-27] Other studies[32] suggested that NSAIDs did not influence the clinical efficacy of antidepressants. On the contrary, observational studies of frequently used NSAIDs observed worse antidepressant treatment effects in clinical,[8] animal,[8] and epidemiologic[9] settings. Observational studies contain the potential for confounding by indication and misclassification of concomitant exposure to antidepressants and NSAIDs compared with randomized studies. Subanalyses emphasized the antidepressant effects of selective COX-2 inhibitors[9]; it seems important to differentiate between single NSAIDs regarding possible antidepressant effects. All randomized studies[6,25-27] emphasized the adjunctive antidepressant effects of celecoxib within the first 6 to 8 weeks of antidepressant treatment, which have been suggested[25] to be most pronounced among patients with increased proinflammatory markers.

To our knowledge, the present study is the first to analyze the overall effect and emphasize the potential antidepressant treatment effects of celecoxib, with and without concomitant antidepressant medication. The effect is considered large and thus clinically relevant. The potential importance of an active inflammatory state on the antidepressant effects of anti-inflammatory agents is supported by studies[14,33] on selective COX-2 inhibitor monotherapy among patients with osteoarthritis. In one trial,[28] 12 months of monotherapy with celecoxib or naproxen in healthy individuals 70 years or older did

Figure 3. Results of Adverse Effects

Source	Treatment Events	Treatment Total	Placebo Events	Placebo Total	OR IV, Randomized, 95% CI
GI symptoms					
Abbasi et al,[25] 2012	3	19	2	18	1.50 (0.22 to 10.22)
Akhondzadeh et al,[26] 2009	2	19	4	18	0.41 (0.07 to 2.59)
Iyengar,[14] 2013	62	1357	14	339	1.11 (0.61 to 2.01)
Subtotal (95% CI)		**1395**		**375**	**1.04 (0.61 to 1.79)**
Total events	67		20		
Heterogeneity: τ^2=0.00; χ^2_2 1.16 (P=.56); I^2=0%					
Test for overall effect: z=0.16 (P=.87)					
Infections					
Menter et al,[29] 2010	0	44	0	52	Not estimable
Raison et al,[24] 2012	4	30	2	30	2.15 (0.36 to 12.76)
Tyring et al,[7] 2006	87	305	71	292	
Subtotal (95% CI)		**379**		**374**	**1.27 (0.89 to 1.82)**
Total events	91		73		
Heterogeneity: τ^2=0.00; χ^2_1=0.35 (P=.55); I^2=0%					
Test for overall effect: z=1.31 (P=.19)					
Cardiovascular adverse effects					
Iyengar et al,[14] 2013	8	1357	1	339	2.00 (0.25 to 16.08)
Subtotal (95% CI)		**1357**		**339**	**2.00 (0.25 to 16.08)**
Total events	8		1		
Heterogeneity: Not applicable					
Test for overall effect: z=1.65 (P=.51)					



GI indicates gastrointestinal; OR, odds ratio.

Table 2. Quality of Reporting, Indicating High or Low Risk of Bias for the Investigated Trials in 5 Domains

Source	Allocation: Sequence Generation	Allocation: Concealment	Blinded Outcome Assessment	Intention-to-Treat Analysis	For-Profit Bias
Tyring et al,[7] 2006	High	Low	Low	High	High
Langley et al,[30] 2010	High	High	Low	High	High
Fields et al,[28] 2012	High	High	Low	High	High
Menter et al,[29]2010	High	High	Low	High	High
Raison et al,[24] 2012	Low	High	Low	Low	High
Abbasi et al,[25] 2012	Low	Low	Low	High	Low
Akhondzadeh et al,[26] 2009	Low	High	Low	High	Low
Hashemian et al,[27] 2011	High	High	Low	High	High
Müller et al,[6] 2006	High	High	Low	High	High
Iyengar et al,[14] 2013[a]					
A3191051	High	High	Low	High	High
A3191052	High	High	Low	High	High
A3191053	High	High	Low	High	High
A3191062	High	High	Low	High	High
A3191063	High	High	Low	High	High

[a] The study was a meta-analysis of 5 trials investigating nonsteroidal anti-inflammatory monotherapy. The trials (A3191051, A3191052, A3191053, A3191062, and A3191063) are presented individually.

not improve depressive symptoms. These findings on the potential antidepressant effects of celecoxib are supported by animal studies[34] and 2 recent meta-analyses that investigated celecoxib as add-on treatment[13] and monotherapy.[14]

Few studies have investigated the potential antidepressant effects of cytokine inhibitors. Findings have included improvement of depression[7,29,35] and specific depressive symptoms, such as anxiety[30] and fatigue,[7] among patients with psoriasis[7,29,30] or ankylosing spondylitis,[35] which is supported by animal models.[36] However, the presence of depression has been found to reduce the rate of remission with infliximab treatment in patients with Crohn disease.[37] Only 4 randomized placebo-controlled trials evaluating cytokine inhibitors could be included in the present meta-analysis, showing a trend toward superiority compared with placebo. The study by Raison et al[24] was the only one that did not note an overall association of infliximab with antidepressant effects; however, in the subgroup with increased CRP levels, infliximab

mab improved the antidepressant response. Thus, our results on cytokine inhibitors must be regarded as preliminary owing to the limited number of studies. However, the findings emphasize a potential effect and support the need for studies to further specify the suggested effects of cytokine inhibitors on different subgroups (eg, patients with increased proinflammatory markers).

Adverse Effects of Anti-inflammatory Agents

The potential antidepressant treatment effects of anti-inflammatory strategies should always be balanced against the risk for adverse effects. Nonsteroidal anti-inflammatory drugs increase the risk for gastrointestinal[10] and cardiovascular adverse effects,[11] whereas cytokine inhibitors increase the risk for infections.[12] We observed no increased risks of these important adverse effects; however, not all of the studies included in the present meta-analysis reported on adverse effects and treatment lasted only 6 to 12 weeks (Table 1), which potentially is too short to detect relevant adverse effects. Evaluation is particularly important concerning selective COX-2 inhibitors, with some withdrawn from the market because of their increased risks for cardiovascular events. Other studies have suggested that celecoxib may be safer as monotherapy compared with other selective COX-2 inhibitors[38] without an increased risk when used as add-on therapy in the early phase of antidepressant treatment.[6] Still, our results on celecoxib should be interpreted cautiously, since not all studies reported on adverse effects.

Other Agents With Possible Anti-inflammatory Potential

Other anti-inflammatory agents may have antidepressant effects, but no studies met the inclusion criteria for the meta-analysis. Aspirin has been associated with adjunctive antidepressant treatment effects, even at low doses.[39] Statins[40] and the tetracycline antibiotic minocycline[41] may have antidepressant treatment effects. Minocycline is also interesting, since it crosses the blood-brain barrier more easily than other antibiotics.[42] However, statins have many effects other than anti-inflammatory. No randomized placebo-controlled trials have evaluated the antidepressant effects of minocycline or aspirin. Recent reviews emphasized aspirin because of a more favorable benefit to risk ratio[43] and potentially better antidepressant effects compared with those of selective COX-2 inhibitors.[44]

Polyunsaturated fatty acids,[45] the antidiabetic drug pioglitazone,[46,47] the vigilance-augmenting drug modafinil,[48] and modulation of the mineralocorticoid receptor[49] also improved the effects of antidepressants in randomized, placebo-controlled trials. However, the anti-inflammatory effects of these agents are speculative and were therefore not included in the present meta-analysis. Synthetic cortisol compounds have shown acute antidepressant effects,[50,51] but because of cortisol's various effects, these results cannot exclusively be ascribed to an anti-inflammatory effect.

Perspectives

Compelling evidence suggests an association between depression and inflammation, but no causal link with specific inflammation markers, such as CRP, has been established.[52] Research should be prioritized to identify markers and the underlying cellular mechanisms to support identification of relevant subgroups that would benefit from anti-inflammatory treatment or potentially new antidepressant drugs with a targeted effect on inflammation. Different approaches are of particular interest. First, subgroups of depressed patients with elevated inflammatory markers (CRP and IL-6) have been associated with higher rates of treatment response.[24,25] Second, patients with depressive symptoms as well as comorbid pain-related[14,33] or inflammatory[7,29,30] disorders responded better to anti-inflammatory treatment. Third, it should be further elucidated whether anti-inflammatory treatment effects could be linked to a reduction of specific depressive symptoms.

Finally, it is interesting that NSAIDs, particularly celecoxib, have been associated with treatment effects in schizophrenia[53,54] and bipolar disorder.[55] This association indicates that immune-related factors might be implicated and that anti-inflammatory treatment strategies would be relevant to evaluate in a larger spectrum of psychiatric disorders.

Conclusions

Our results indicate a proof-of-concept concerning the use of anti-inflammatory agents in the antidepressant treatment regimen and thus provide support for the speculated link between inflammation and subgroups of patients with major depressive disorder. In this meta-analysis, the use of NSAIDs was associated with an improved antidepressant treatment response without an increased risk for well-known adverse effects. In particular, add-on treatment with celecoxib improved antidepressant effects, remission, and response. Cytokine inhibitors were studied in few trials, and no significantly better antidepressant treatment effects were found compared with placebo.

Our findings emphasize the need for identifying subgroups that may benefit more from anti-inflammatory intervention, such as patients with elevated inflammatory markers or a somatic comorbidity. Specific agents, particularly celecoxib, showed promising results and should therefore be investigated in high-quality randomized clinical trials. Such trials should carefully report on adverse effects and include long-term follow-up.

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Study concept and design: Köhler, Benros, Krogh.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Köhler, Benros, Farkouh, Iyengar.
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