ARTICLE

Effect of Anti-Inflammatory Treatment on Depressive Symptom Severity and Anhedonia in Depressed Individuals With Elevated Inflammation: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objective: Studies evaluating the effect of anti-inflammatory treatment on depressive symptom severity and anhedonia in depressed individuals report mixed results. In this preregistered systematic review and meta-analysis, the authors evaluated whether anti-inflammatory treatments, compared to placebo, reduce anhedonia and depressive symptom severity in depressed individuals with an inflammatory phenotype.

Methods: The authors included randomized controlled trials of pharmacological anti-inflammatory treatments that assessed anhedonia or depressive symptom severity and recruited depressed individuals with an inflammatory phenotype or measured baseline inflammatory biomarkers that permitted post hoc analysis. A search was conducted in February 2025 of MEDLINE, Embase, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and PsycINFO. Multiple reviewers independently applied criteria, and discrepancies were resolved via consensus. Two reviewers independently extracted data and cross-checked for errors.

Results: In randomized controlled trials (k=11) using an established cutoff for elevated inflammation (C-reactive protein ≥2 mg/L), both anhedonia (Hedges' g=0.40, 95% CI=0.08, 0.71) and depressive symptoms (Hedges' g=0.35, 95% CI=0.05, 0.64) were reduced, but no differences in treatment response (relative risk=1.28, 95% CI=0.997, 1.64) or remission rates (relative risk=1.18, 95% CI=0.71, 1.95) were observed. Results did not vary by clinical, interventional, or demographic characteristics.

Conclusions: Anti-inflammatory treatments may be safe and effective at reducing depressive symptoms and anhedonia in depressed individuals with heightened inflammation. Not accounting for inflammatory status may help explain prior mixed findings.

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Depression is the leading cause of the mental health–related global disease burden, affecting 400 million individuals worldwide and accounting for 40% of total days lost to poor mental health (1, 2). Approximately 65% of individuals will not achieve remission after a first-line antidepressant treatment, and one-third will not achieve remission following multiple treatments (3). Novel, efficacious antidepressant treatments are urgently needed.

Convergent evidence based on genetic and multiomics studies (4, 5), experimental research (6), and observational studies (7–11) suggests that a subtype of depression—inflammatory depression—is characterized by dysregulated immune physiology and occurs in ~25% of cases (for reviews, see 12, 13). Circulating levels of inflammatory biomarkers (e.g., C-reactive protein [CRP], an acute phase protein synthesized by the liver in response to tissue damage or pathogens) are routinely elevated in depressed individuals compared to healthy control subjects, are highly associated with levels of other inflammatory mediators in the peripheral blood and cerebrospinal fluid (14), and are predictive of future depression (7). Moreover, experimental induction of an innate immune response is reliably associated with onset of depressive symptoms (i.e., total depression score) (15), and inhibiting inflammatory signaling in patients with

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inflammatory disorders reduces depressive symptoms above and beyond treatment-related changes in physical health (16). There is emerging evidence that dysregulated inflammatory physiology is associated with a specific clinical presentation characterized by neurovegetative symptoms and anhedonia (12, 17).

Meta-analyses have previously found that anti-inflammatory treatments are safe and reduce depressive symptoms in individuals experiencing comorbid medical conditions (e.g., rheumatoid arthritis) (18–20). Considerably less is known about the efficacy of anti-inflammatory treatments in depressed individuals without comorbid medical conditions, and initial randomized controlled trials (RCTs) have produced mixed results (18–24). A recent review highlighted two potential causes of mixed results (25). First, many RCTs have not recruited depressed individuals who exhibit an inflammatory phenotype (frequently indexed as CRP levels greater than 2 or 3 mg/L) (26–28) and who are therefore most likely to respond to anti-inflammatories (21, 23, 29). Second, many RCTs do not assess a dimension of depressive symptomatology that is particularly associated with inflammation: anhedonia. Data support a cause-and-effect relationship between increased immune activation and anhedonia (12); however, null results have also been reported (30), and RCTs focusing on the effect of anti-inflammatory agents on anhedonia in depression are relatively sparse (25). Experimental human research has demonstrated that a lipopolysaccharide inflammatory challenge differentially increases anhedonia in depressed individuals with CRP levels ≥3 mg (31). It should be noted that the association of inflammation and anhedonia is overwhelmingly based on measures of consummatory pleasure, and less is known about inflammation's impact on motivational anhedonia (for reviews on anhedonia in depression, see 32, 33; for reviews on inflammation and anhedonia, see 34, 35). Thus, further work is needed to determine whether anti-inflammatory treatment is effective in inflammatory depression and whether we can observe a stronger effect of anti-inflammatory agents on anhedonia compared to overall depressive symptom severity.

This systematic review and meta-analysis is, to our knowledge, the first to examine the effect of anti-inflammatory medications, compared to placebo, on anhedonia and depressive symptom severity in depressed individuals exhibiting an inflammatory phenotype and without medical comorbidity. Secondary outcomes included treatment response, remission status, mortality, and report of serious adverse events at study endpoint. Potential demographic, clinical, and interventional moderators were also investigated.

METHODS

This protocol was preregistered with Prospero (CRD42023472023) and adheres to PRISMA 2020 guidelines (36) (see Table S1 in the online supplement for adherence details).

Eligibility Criteria

Studies were included if they 1) were RCTs; 2) measured anhedonia or depressive symptoms via clinician assessment or self-report; 3) were available in English; 4) recruited for clinical or subclinical depression; 5) recruited for inflammatory phenotype (e.g., CRP level ≥2 mg/L) or measured baseline inflammatory biomarkers that permitted post hoc analysis in depressed individuals with an inflammatory phenotype; and 6) administered a pharmacological anti-inflammatory treatment either as monotherapy or as adjunctive therapy. Studies were excluded if 1) they were not conducted in adults, 2) data were unavailable in reports and authors did not provide data after two contact attempts, 3) the control condition had anti-inflammatory potential (e.g., sustained exercise), 4) participants were recruited on the basis of somatic disease (e.g., rheumatoid arthritis), or 5) patients were undergoing a medical treatment that might cause depression or anhedonia.

Minor deviations from our registered protocol occurred: Studies that included a subset of individuals diagnosed with bipolar I or II disorder were permitted, and studies were included even if participants were not on a stable dosage of psychiatric medication for at least 4 weeks, because this was effectively controlled for by comparison of placebo to treatment. When multiple articles reported on the same RCT, we used the report that was most aligned with our question of interest.

Information Sources and Selection Process

A medical librarian conducted an electronic search, unrestricted by language or dates, in December 2023 (updated in February 2025) using MEDLINE (via Ovid), Embase (Elsevier), Web of Science Core Collection, Cochrane Central Register of Controlled Trials (via Ovid), PsycINFO (via Ovid), and ClinicalTrials.gov. The search strategy incorporated controlled vocabulary and free-text synonyms and was designed to identify RCTs in which medications that target immune function were delivered to depressed individuals exhibiting an inflammatory phenotype, as indexed by immune biomarkers. The full database search strategies are documented in the online supplement. A validated RCT filter was applied and authors (A.A.M., E.L.Q., N.M.G.) reviewed the remaining titles, abstracts, and full-text reports (37). At each stage, each study received independent ratings from two authors; discrepancies were resolved via consensus.

Data Collection

Two authors (N.M.G., A.A.M.) independently extracted data, and a third author (E.L.Q.) checked the quality of the resultant dataset. Primary outcomes of interest were change in anhedonia and change in total depressive symptom severity from baseline to study endpoint. When a study featured multiple intervention or control groups, a comparison was selected to prioritize a clear contrast of anti-inflammatory treatment versus placebo, the most potent anti-inflammatory condition, and the largest sample size. Additional outcomes were depression remission and response rates at study endpoint, prevalence of serious adverse events after randomization, and change in inflammatory

biomarkers. The definitions of remission and response we used were those used in the individual studies. When raw data were analyzed, response was defined as a reduction ≥50% in depressive symptom severity and remission was defined as the standard cutoff for each measure (e.g., Hamilton Depression Rating Scale score ≤7). Target engagement was estimated by categorizing the decrease across inflammatory biomarkers: consistent decrease, inconsistent decrease, or no decrease; given the small number of studies, consistent and inconsistent target engagement were combined in analyses. When raw data were available, we undertook analyses following best-practice guidelines (38). When requesting information, we contacted first and last authors twice via e-mail, social media, or both. When available, intent-to-treat data were preferred above per-protocol analyses. Critical information extracted included author; year of publication; clinical trial registration number; anti-inflammatory agent, dosage, and duration; monotherapy or augmentation; analytic sample size; demographic characteristics (e.g., age, sex, and race); clinical information (e.g., body mass index [BMI], treatment resistance status, and diagnostic status); outcome measurements; and the definition used to operationalize elevated inflammatory status (e.g., CRP ≥2 mg/L).

Bias Assessment

Two authors (N.M.G., A.A.M.) independently used version 2 of the Cochrane risk-of-bias tool for randomized trials (39) to assess study quality; discrepancies were resolved via consensus. See Table S2 in the online supplement for risk-of-bias assessment. For studies in which analyses were reconducted by the authors, analyses were considered prespecified (item 5 in the risk-of-bias tool).

Statistical Analysis

We used the R package *meta* for analyses and visualization (40). For placebo and intervention arms, change in symptom severity from baseline to study endpoint was used for continuous measures and standardized mean difference estimated using Hedges' g; binary and percentage outcomes were converted to proportions and examined in terms of relative risk. Given the studies' methodological heterogeneity, we used random-effects models to examine treatment-related differences in the outcomes (e.g., anhedonia, depressive symptom severity). Eleven studies either had baseline data on CRP levels available, allowing us to limit analyses to participants with CRP levels ≥2 mg/L, or recruited only those with CRP levels ≥2 mg/L. We chose a CRP level ≥2 mg/L as a cutoff because it is more inclusive than a cutoff of ≥3 mg/L and still fulfills the critical criterion of representing clinically significant inflammation, as indicated by updated American Heart Association guidelines (41) and widespread use in clinical studies (26, 42, 43). Cochran's Q and the inconsistency index estimated statistical heterogeneity. Publication bias was visually assessed with a funnel plot and statistically assessed with Egger's regression intercept test. Missing descriptive statistics were, as appropriate, estimated using Cochrane review guidelines (38). Secondary analyses (meta-regression for binary variables and subgroup analyses for categorical variables) explored whether the treatment's effect depended on intervention characteristics (drug class, target engagement [i.e., whether inflammation decreased]), monotherapy versus add-on therapy, risk-of-bias status (high versus low/some concerns), sociodemographic characteristics (age, sex, race), and clinical characteristics (treatment-resistant depression [TRD] versus non-TRD, BMI).

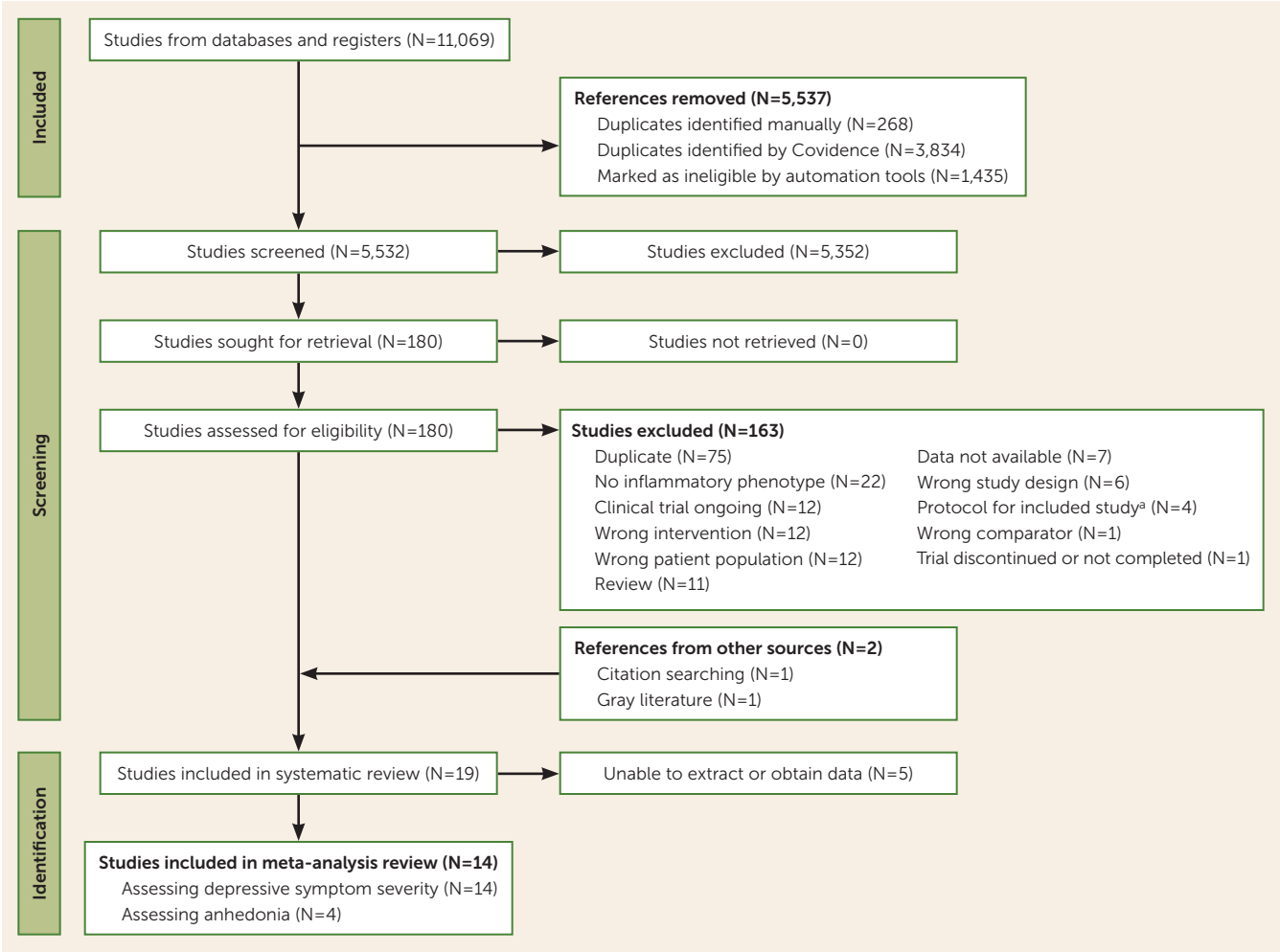
RESULTS

Search results are presented in a PRISMA flow diagram (Figure 1). From the initial 11,069 results, 5,532 unique studies were screened for eligibility. Following title and abstract review, 180 papers were included for full-text review. An additional 163 studies were subsequently removed; aggregate reasons for exclusions are detailed in Figure 1. One additional relevant study was added following review of reference lists (29). Additionally, one already-included report featured results from two studies (44). Thus, 19 studies were included in the systematic review (44–47), and 14 of these studies were included in the meta-analysis (21, 23, 24, 29, 48–57). Analyses primarily focus on 11 of these studies that used an established clinical cutoff for low-grade inflammation (CRP level ≥2 mg/L).

Key characteristics of the 19 RCTs are described in Table 1. These 19 RCTs evaluated the efficacy of anti-inflammatory medications, including interleukin-6 inhibitors (k=2), mitogen-activated protein kinase inhibitors (k=2), minocycline (k=5), nonsteroidal anti-inflammatory drugs (NSAIDs) (k=5), recombinant interleukin-2 (k=1), and tumor necrosis factor (TNF) inhibitors (k=4). All RCTs compared anti-inflammatory drugs to placebo. Treatment duration ranged from 2 to 12 weeks. Overall, a majority of RCTs in the review did not recruit for TRD (k=14) and used anti-inflammatories as adjunctive treatments (k=13). Seven of the 14 RCTs in the meta-analysis recruited patients with an inflammatory phenotype (i.e., enriched sample), although there was substantial variation in terms of how that was defined. Eleven of the 14 RCTs permitted analysis of a subgroup with an established cutoff point (CRP level ≥2 mg/L).

In studies using a CRP cutoff of at least ≥2 mg/L (k=11), anti-inflammatory treatment led to a reduction in anhedonia (k=4, N=163; Hedges' g=0.40, 95% CI=0.08, 0.71, p=0.013) and depressive symptom severity (k=11, N=321; Hedges' g=0.35, 95% CI=0.05, 0.64, p=0.022) when compared to placebo (Figure 2). No significant difference in the occurrence of serious adverse events was reported in the inflammatory and placebo groups (k=10; relative risk [RR]=1.08, 95% CI=0.35, 3.39, p=0.89; I^2=0%), and mortality was not reported in any study in either group. Anti-inflammatory treatment compared to placebo was not significantly associated with greater likelihood of treatment response (average weighted treatment response rate: anti-inflammatory condition, 49%; placebo condition, 41%; k=8; RR=1.27, 95% CI=0.997, 1.61, p=0.053; I^2=0%) or remission (average weighted treatment remission rate: anti-inflammatory condition, 23%; placebo condition, 21%; k=7; RR=1.20, 95% CI=0.74, 1.96, p=0.46; I^2=0%). Rates of

FIGURE 1. PRISMA flow diagram showing the number of studies excluded at each stage of the systematic review as well as the rationale for exclusion



[a]This indicates published protocols for research studies that have published results that have already been included in the systematic review.

serious adverse events, mortality, and discontinuation due to adverse events are listed in Table S3 in the online supplement.

In studies (k=14) using a larger range of cutoffs to define an inflammatory phenotype (e.g., median split), no difference across results was observed when compared to studies using a stricter cutoff (i.e., CRP level ≥2 mg/L), although the magnitude of reduction in depressive symptom severity was lower (k=14, N=376; Hedges' g=0.26, 95% CI=0.01, 0.51, p=0.039; I^2=23.3%). Similarly, when using a more conservative range to define an inflammatory phenotype (i.e., CRP level ≥3 mg/L), no difference across results was observed compared to studies using more liberal cutoffs (e.g., CRP level ≥2 mg/L), although the magnitude of reduction in depressive symptom severity was lower (k=10, N=310; Hedges' g=0.28, 95% CI=0.01, 0.55, p=0.04; I^2=22.6%). All studies reporting on anhedonia used a CRP cutoff of at least ≥3 mg/L.

Complete results of meta-regression and subgroup analyses are reported in the online supplement. Additional demographic and clinical information extracted from studies are provided in Table S4 in the online supplement. The treatment's effect compared to placebo was not moderated by treatment-resistant status, administration as adjunctive treatment versus monotherapy, drug class, or level of target engagement (treatment-resistant status: k=11; Q=0.99, p=0.32; I^2=34.56%; TRD Hedges' g=0.60, 95% CI=−0.04, 1.25; I^2=49.20%; non-TRD Hedges' g=0.23, 95% CI=−0.08, 0.55; I^2=23.50%; administration as adjunctive treatment: k=11; Q=0.66, p=0.42; I^2=39.03%; adjunctive Hedges' g=0.15, 95% CI=−0.29, 0.59; I^2=0.00%; monotherapy Hedges' g=0.47, 95% CI=0.05, 0.88; I^2=51.10%; drug class: k=11; Q=1.59, p=0.45; I^2=39.80%; cytokine modulator Hedges' g=0.32, 95% CI=−0.04, 0.68; I^2=30.90%; minocycline Hedges' g=0.71, 95% CI=−0.21, 1.64; I^2=65.30%; NSAID Hedges' g=0.04, 95% CI=−0.51, 0.60; I^2=0.00%; level of target engagement: k=10; Q=0.40, p=0.53; I^2=40.11%; consistent/inconsistent target engagement Hedges' g=0.49, 95% CI=0.09, 0.90; I^2=25.10%; no target engagement Hedges' g=0.29, 95% CI=−0.38, 0.97; I^2=55.10%).

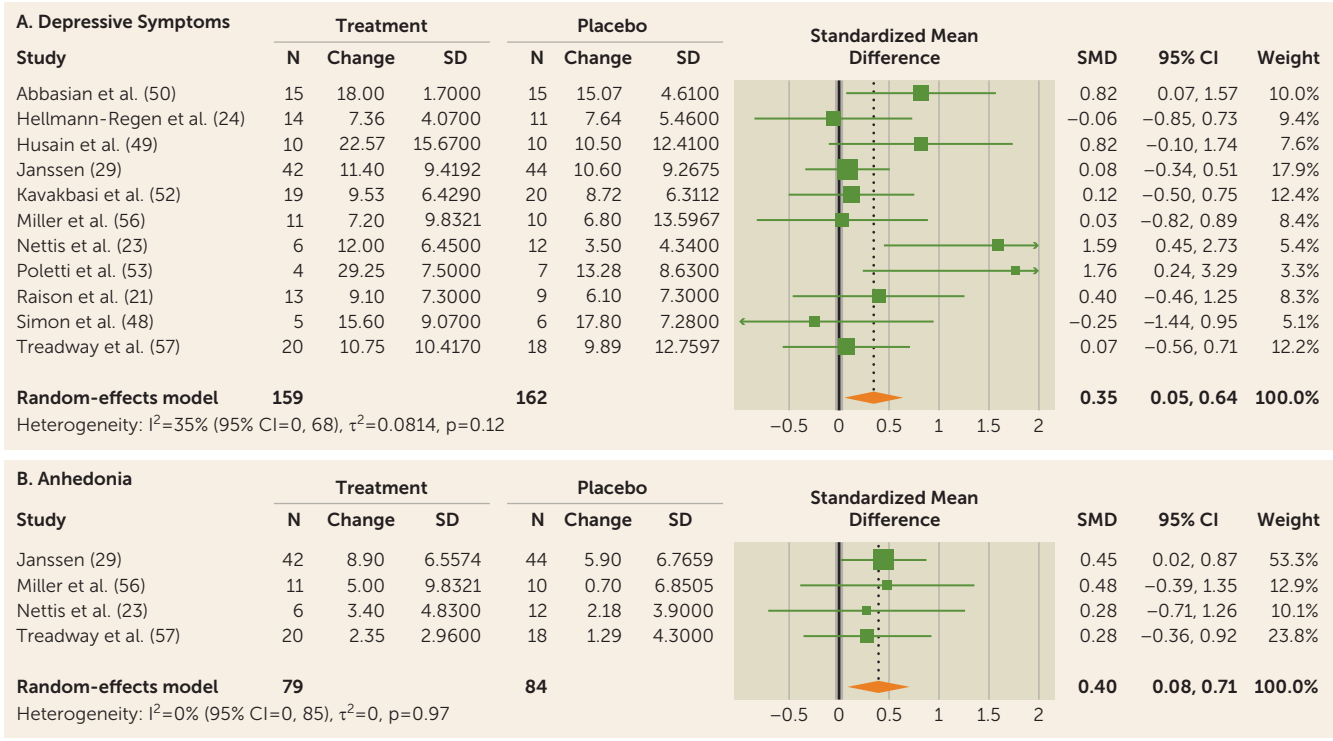
RCTs exhibited low risk (N=4), some concerns (N=8), and high risk (N=7) when evaluated using version 2 of the

TABLE 1. Study characteristics of all clinical trials included in the systematic review[a]

Author (reference)	In meta-analysis	Medication	Dosage	Duration (weeks)	Adjunctive or Monotherapy	Analytic Sample (N)	Inter-vention (N)	Placebo (N)	Mean age (years)	Female (%)	White (%)	BMI (mean)	TRD	Depression measure	Anhedonia measure	Enriched or subgroup	Inflammatory subtype definition
Raison et al. (21)	Yes	Infliximab	5 mg/kg	12	Monotherapy	22	13	9	43.40	67.00	77.00	31.95	Yes	HAM-D		Subgroup	CRP≥5 mg/L
Nettis et al. (23)	Yes	Minocycline	200 mg	4	Adjunctive	18	6	12	45.22	56.41	84.58	31.32	Yes	HAM-D	SHAPS	Subgroup	CRP≥3 mg/L
Simon et al. (48)	Yes	Celecoxib	200 mg	6	Adjunctive	11	5	6	40.45	36.00		25.36	No	MADRS		Subgroup	CRP≥3 mg/L
Husain et al. (49)	Yes	Minocycline	200 mg	12	Adjunctive	20	10	10	37.60	45.00	0.00	24.72	Yes	HAM-D		Subgroup	CRP≥5 mg/L
Treadway et al. (57)	Yes	Infliximab	5 mg/kg	2	Monotherapy	38	20	18	39.03	88.10	42.90	33.46	No	HAM-D	MDFI-RM	Enriched	CRP≥3 mg/L
Abbasian et al. (50)	Yes	Adalimumab	5 mg/kg	6	Adjunctive	30	15	15	35.24	56.66			No	HAM-D		Enriched	CRP≥3 mg/L
Hasebe et al. (51)	Yes	Minocycline	200 mg	12	Adjunctive	27	14	13	49.48	66.21		29.70	No	MADRS		Subgroup	IL-6 median split
Inamdar et al. study 1 (44)	No	Losmapimod	7.5 mg	6	Monotherapy								No				
Inamdar et al. study 2 (44)	No	Losmapimod	7.5 mg	6	Monotherapy								No				
Kavakbasi et al. (52)	Yes	Celecoxib	400 mg	6	Adjunctive	39	19	20	51.51	71.62		33.28	No	HAM-D		Enriched	CRP≥3 mg/L
Musil et al. (45)	No	Celecoxib	400 mg	6	Adjunctive								No				
Poletti et al. (53)	Yes	Aldesleukin	1 M IU	8.57	Adjunctive	11	4	7	43.64	63.40	100.00	26.56	No	MADRS		Subgroup	CRP≥2 mg/L
Abbasi et al. (46)	No	Celecoxib	400 mg	6	Adjunctive								No				
Dodiya et al. (47)	No	Aceclofenac	200 mg	12	Adjunctive								No	HAM-D		Subgroup	IL-6≥6 pg/mL
Miller et al. (56)	Yes	Infliximab	5 mg/kg	2	Monotherapy	21	11	10	38.60	86.40	50.00		No	IDS-SR	SHAPS	Enriched	CRP≥3 mg/L
Attwells et al. (54)	Yes	Minocycline	200 mg	8	Adjunctive	21	12	9	51.43	71.42	76.19	24.87	Yes	HAM-D		Enriched	TSPO in PFC, ACC, insula
Hamilton et al. (55)	Yes	Tocilizumab	162 mg	4	Monotherapy	7	4	3					No	MADRS		Enriched	IL-6>1.5 ng/L
Hellmann-Regen et al. (24)	Yes	Minocycline	200 mg	6	Adjunctive	25	14	11	48.08	56.00	94.64	30.98	Yes	HAM-D		Subgroup	CRP≥3 mg/L
Janssen (29)	Yes	Sirukumab	50 mg	12	Adjunctive	86	42	44	44.70	77.20	89.60		No	HAM-D	SHAPS	Enriched	CRP≥3 mg/L

[a] Sample size and demographic information are reported only for studies included in the quantitative analysis. ACC, anterior cingulate cortex; CRP, C-reactive protein; HAM-D, Hamilton Depression Rating Scale; IDS-SR, Inventory for Depressive Symptomatology–Self Report; IL-6, interleukin-6; MADRS, Montgomery-Åsberg Depression Rating Scale; MDI-RM, Multidimensional Fatigue Inventory-Reduced Motivation subscale; PFC, prefrontal cortex; SHAPS, Snaith-Hamilton Pleasure Scale; TPSO, translocator protein.

FIGURE 2. Forest plots displaying effect of anti-inflammatory treatments on anhedonia and depressive symptoms[a]



[a]SMD=standardized mean difference.

Cochrane risk-of-bias tool. Visual inspection of funnel plots did not provide evidence of asymmetrical results for anhedonic symptoms. However, results appeared somewhat asymmetrical for depressive symptoms, with two notably large effects from small trials (see Figure S1 in the online supplement). Egger's regression test could not be performed for anhedonic symptoms and was not statistically significant using a CRP cutoff of ≥2 mg/L (t=2.11, df=9, p=0.065), a cutoff of ≥3 mg/L (t=1.38, df=8, p=0.21), or a wider range of cutoffs (t=1.61, df=12, p=0.13).

DISCUSSION

To our knowledge, this is the first meta-analysis examining the effect of anti-inflammatory treatment, when compared to placebo, on anhedonia and depressive symptom severity among depressed individuals with high levels of inflammation and without somatic disease (i.e., inflammatory depression). We found that anti-inflammatory treatment, when compared to placebo, reduced anhedonia (Hedges' g=0.40, 95% CI=0.08, 0.71) and depressive symptoms (Hedges' g=0.35, 95% CI=0.05, 0.64) in studies that used an established clinical cutoff for inflammation (CRP level ≥2 mg/L). This effect size was substantially higher than the effect size when ad hoc cutoffs for inflammation were employed (Hedges' g=0.26, 95% CI=0.01, 0.51), but it may have been driven by large effect sizes observed across a modest number of small-sample RCTs. No difference in the prevalence of serious adverse events for anti-inflammatory treatments versus placebo was observed. Rates of treatment response and remission were not increased among individuals receiving anti-inflammatory treatment, although response rates were numerically and substantively higher. These results should be considered preliminary given the heterogeneity of effect sizes for depressive symptom severity, the small numbers of studies, and the small sample sizes, but they indicate that anti-inflammatory agents are safe and effective in reducing depressive symptoms and anhedonia in inflammatory depression.

That anti-inflammatory treatment is effective at reducing symptoms of anhedonia and depressive symptom severity in depression is consistent with some results from prior RCTs in both unipolar and bipolar depression (29, 58). However, it is important to note that there was considerable heterogeneity in the effect of anti-inflammatory treatment on depressive symptom severity. Indeed, the three largest studies (29, 52, 57) reported very small effect sizes (Cohen's d<0.12), and the observed effect size for depressive symptom severity was driven by a modest number of small-sample RCTs. In contrast, the effect of anti-inflammatory treatment on anhedonia was larger and considerably more consistent when compared to overall depressive symptoms. A specific effect of anti-inflammatory treatment on anhedonia is consistent with data from animal and human studies across a range of modalities and research designs demonstrating the sensitivity of reward circuitry to peripheral pro-inflammatory immune signaling (34, 35, 59–61). However, most RCTs (~70%) did not examine the effect of anti-inflammatory treatment on anhedonia, and the most common measure of anhedonia used (the

Snaith-Hamilton Pleasure Scale) primarily assesses consummatory pleasure to the exclusion of anticipatory anhedonia and motivation (62). Thus, further work is needed that 1) confirms the potential of anti-inflammatory treatment to target anhedonia in depression, 2) captures the multidimensional nature of anhedonia and can meet regulatory requirements needed to serve as clinical outcome assessments in trials sponsored by the U.S. Food and Drug Administration (63), 3) better characterizes other symptoms likely associated with inflammatory depression (fatigue, psychomotor slowing) (17), and 4) characterizes the multiple pathways leading to anhedonia in depression (62). Further, this pattern of results suggests that future studies may benefit from enriching for anhedonia as well as an inflammatory phenotype, as the two may better represent a subpopulation likely to respond more strongly to anti-inflammatory treatment.

The effect of anti-inflammatory treatment on anhedonia and depressive symptom severity was substantially stronger in studies that enriched for high levels of inflammation using an established clinical cutoff. This finding aligns with prior studies (21, 23, 29) and reinforces the need for clinical trial designs that include subjects with increased inflammation (25). These effects were observed across studies using a CRP cutoff of ≥2 mg/L (although a cutoff of ≥3 mg/L is also commonplace [57]) and support the utility of CRP as a biomarker to enrich clinical trials. CRP is an affordable, accessible, and sensitive measure of peripheral inflammation with established clinical cutoffs, and it is strongly correlated with neuroinflammation (64). However, CRP exhibits undesirable qualities: 1) it may not be as stable as often assumed (65); 2) its clinical cutoffs were established using a small, nonrepresentative dataset (see reference 27 for a review); 3) it is associated with adiposity in a sex-specific manner (66); and 4) it is highly nonspecific in nature, capturing systemic immune activation rather than identifying pathogenic processes causally related to depression (67). Thus, even though CRP may be useful as a stratification tool, an ideal biomarker would be more reliable, less confounded, and a specific marker of the underlying immune-based mechanism.

Overall, these results do not differ in relation to a variety of clinical, intervention, and demographic characteristics; however, statistical power to detect moderation was limited (≤11 studies). Effect sizes were numerically and substantively higher for studies with lower risk of bias (Hedges' g=0.46, 95% CI=−0.20, 1.13), TRD (Hedges' g=0.60, 95% CI=−0.04, 1.25), specific anti-inflammatory agents (cytokine modulators Hedges' g=0.32, 95% CI=−0.04, 0.68; minocycline Hedges' g=0.71, 95% CI=−0.21, 1.64), and some level of target engagement (inconsistent/consistent target engagement Hedges' g=0.49, 95% CI=0.09, 0.90). Variability in results may be partially explained by differences in the specificity or potency of anti-inflammatory medications deployed and resultant capacity to modulate immune function in depressed individuals. In addition to more reliable biomarkers of inflammatory depression and better characterization of the underlying immune-based mechanism, a central focus of immunopsychiatry must be to identify the appropriate medication (as well as dosage and duration) that can target dysregulated inflammatory physiology and deliver therapeutic benefit in inflammatory depression (68–70).

This systematic review suggests that anti-inflammatory treatments may effectively reduce depressive symptoms and anhedonia among individuals with an inflammatory phenotype. It reinforces the importance of considering a precision medicine approach targeting depressive symptoms (71). Clinically, the risk of a nonspecific approach (e.g., failure to directly target inflammation in a patient in whom inflammation is a primary etiological factor of depression) may greatly delay delivery of effective treatment. Anti-inflammatory treatments have potential to augment existing treatment strategies; however, gaps in fundamental knowledge must first be addressed. In addition to a dearth of well-powered studies recruiting on the basis of elevated inflammation, this review highlights multiple sources of heterogeneity in medications used (as well as dosage and duration), enrollment inclusion and exclusion criteria, and target engagement. A better understanding of the requisite dosage and duration of a specific medication that will meaningfully reduce levels of systemic inflammation and exert antidepressant effects is a prerequisite to their integration in clinical practice (see references [63, 72] for recent reviews on potential integration of inflammatory depression within clinical practice and design of future clinical trials).

In interpretating these results, study limitations should be borne in mind. First, confidence intervals were broad and individual study samples were small (particularly for anhedonia and in moderation analyses); consequently, the findings of this meta-analysis require replication using better-powered RCTs (73). Second, many studies had a high risk of bias. A common reason is that trials did not recruit for an inflammatory phenotype and/or results were based on post hoc analyses. Third, the number of studies that reported data on anhedonia as assessed using reliable and validated measures was small, and more work is needed to confirm these results. Further, the included studies did not recruit patients for anhedonia regardless of depression status, so we are unable to speculate as to whether the observed result generalizes to people with anhedonia who do not have depression. We also did not compare the effect of anti-inflammatory treatment on those with CRP levels ≥2 mg/L compared to those with levels <2 mg/L to show that this effect is specific to an inflammatory subtype of depression; yet, the current mixed literature in this domain suggests that failing to target this inflammatory phenotype dilutes the observed effect. Lastly, there was considerable heterogeneity across studies based on inclusion criteria (e.g., inclusion of bipolar depression), study design (e.g., trial length, medication type), and statistical analyses (e.g., use of intent-to-treat analyses). Thus, moderator analysis should be considered as exploratory. Further, this study is unable to assess bias in effect sizes attributable to participant nonadherence. These limitations further highlight the need for additional high-quality RCTs evaluating anti-inflammatory treatments in inflammatory depression.

Taken together, our findings suggest that anti-inflammatory treatments may effectively treat depression and anhedonia in depressed patients who exhibit an inflammatory phenotype (e.g., elevated CRP). The findings highlight the continued relevance of inflammatory physiology as a potential cause of depression as well as a treatment target, as conceived within a precision medicine approach. This systematic review also provides guidance for the design of RCTs that will provide high-quality evidence to inform more precise and effective depression treatment.

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Data sharing: Relevant data and statistical code will be made available upon reasonable written request to the corresponding author.

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Examination Questions for "Effect of Anti-Inflammatory Treatment on Depressive Symptom Severity and Anhedonia in Depressed Individuals With Elevated Inflammation: Systematic Review and Meta-Analysis of Randomized Controlled Trials"

1. **What approximate proportion of individuals with depression is estimated to have an inflammatory subtype?**
   A. 0.1
   B. 0.25
   C. 0.5
   D. 0.75
2. **Anti-inflammatory medications have the numerically strongest and most consistent effect on which clinical feature of depression?**
   A. Overall depressive symptom severity
   B. Negative inferential Style
   C. Anhedonia
   D. Sadness
3. **What are common clinical C-reactive protein cut-offs currently used to identify individuals with "inflammatory depression"?**
   A. 2 or 3 mg/L
   B. 0 or 1 mg/L
   C. 5 mg/L
   D. 10 mg/L