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REVIEW

Anti-Inflammatory Treatment Efficacy in Major Depressive Disorder: A Systematic Review of Meta-Analyses

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Purpose: Immune imbalances in major depressive disorder (MDD) have been targeted by anti-inflammatory treatment approaches in clinical trials to increase responsiveness to therapy. However, even after several meta-analyses, no translation of evidence into clinical practice has taken place. We performed a systematic review to evaluate meta-analytic evidence of randomized controlled trials on the use of anti-inflammatory agents for MDD to summarize efficacy estimates and elucidate shortcomings.

Methods: Pooled effect estimates and heterogeneity indices were primary outcomes. Characteristics of the included meta-analyses were extracted. Scientific quality of meta-analyses was assessed using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR).

Results: N=20 meta-analyses met the eligibility criteria. Study characteristics like outcome scales, composition of patient populations, and add-on or monotherapy regimen varied very little for celecoxib studies, varied little for minocycline studies, and were rather variable for omega 3 fatty acids studies. R-AMSTAR scores ranged from 26 to 39 out of 44 points indicating variable quality, where a comprehensive literature search was the strongest and the consideration of scientific quality in the conclusions was the weakest domain across all meta-analyses. For minocycline and celecoxib, superiority was demonstrated with medium to large effect size with substantial heterogeneity and with large to very large effect size with negligible heterogeneity, respectively. For omega 3 fatty acids, superiority was also demonstrated with mainly small and medium effect sizes with substantial heterogeneity. However, for minocycline and omega 3 fatty acids, non-significant meta-analyses were found also.

Conclusion: Even in our synthesized approach, no clear recommendations could be derived on the use of anti-inflammatory treatment for MDD due to several critical aspects like heterogeneity, diversity of patient populations, treatment regimen, and outcomes, and limited scientific quality. However, we observed clear inter-substance differences with meta-analytic evidence being strongest for celecoxib and weakest for omega 3 fatty acids.

Keywords: major depressive disorder, inflammation, anti-inflammatory therapy, state of knowledge, methodological shortcomings

Introduction

Major depressive disorder is a worldwide health problem. The Global Burden of Diseases, Injuries, and Risk Factors Study shows that depressive disorders rank at 13 in the disability-adjusted life years ranking, where in the younger age groups (10–49 years) they even rank among the top ten.[1] A variety of treatment options have been established, and medication like selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), or serotonin-norepinephrine reuptake inhibitors (SNRIs) are prescribed very often.[2–4] However, the course of disease is often recurring, and a considerable number of patients do not respond to established therapies appropriately.[5–7]

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The most prominent etiological theory is the monoamine hypothesis which proposes a lack of neurotransmitter availability during neurotransmission (specifically serotonin, noradrenaline, and/or dopamine), leading to depressive symptomatology.[8–10] Now a mounting body of evidence supports the role of inflammatory activation and immune deregulations in depression, where several components of the immune system have been investigated. Most studies focused on levels of pro-inflammatory circulating cytokines, many of which were found to be elevated in depression.[11,12] Much attention has also been paid to the kynurenine pathway which is stimulated by pro-inflammatory activation.[13] Neurotoxic kynurenine pathway metabolites are thought to play a role in the pathophysiology of depression, but diverging evidence exists.[13,14] Further, altered lymphocyte apportioning for T regulatory cells, Th2 cells, Th17 cells, T memory cells, and NK cells was found among patients with major depressive disorder.[15–17] Last but not least, low-grade inflammation was also present in the monocyte gene expression signature of such patients.[18] These studies give an impression of the variety of compounds studied and the complexity of assembling the pathophysiological mechanisms of major depressive disorder. So far, no integrative theory exists.

Inflammation has been discussed as a major contributor to non-response to established antidepressants.[19–21] Thus, anti-inflammatory treatment approaches have been introduced and were tested in numerous clinical trials to treat depression. These studies investigated anti-inflammatory agents as single agents or as add-on regimen to standard therapy and in patients diagnosed with major depressive disorder or with depressive symptoms (eg, Freeman et al, Müller et al).[22,23] The investigated agents exhibit their mechanism of action at different points in the pathway of the inflammatory machinery. For example, non-steroidal anti-inflammatory drugs, (NSAID) like the cyclooxygenase (cox)-2 selective NSAID celecoxib, inhibit the enzymes cox while cox-2 is mainly involved in the stimulation of inflammation.[24] Anti-tumor necrosis factor (TNF) antibodies (such as infliximab) directly target and inactivate the pro-inflammatory cytokine TNF.[25] N-acetylcysteine (NAC) reduces reactive oxygen species and oxidative stress and thus has anti-inflammatory properties.[26,27] Minocycline also exerts anti-oxidative and anti-inflammatory properties, but multiple mechanisms are under consideration such as the inhibition of the inflammation stimulating enzymes matrix metalloproteinases, cox-2, and caspase-1.[28,29] Lastly, omega 3 fatty acids also have immune-modulating capacities through multiple mechanisms such as inhibition of cox, pro-inflammatory cytokines, or transcription nuclear factor kappa B.[30] In fact, a reduction of inflammatory parameters in depressed patients after the application of anti-inflammatory treatment has been shown: C-reactive protein (CRP) levels declined from baseline to endpoint during infliximab therapy.[31] However, other studies on macrophage migration inhibitory factor (MIF) during celecoxib treatment, on CRP and interleukin-6 (IL-6) during NAC treatment, or on CRP during minocycline treatment showed no significant change or even an increase in their levels.[20,32–34] This demonstrates the complexity of underlying mechanisms in that the choice of inflammatory biomarkers may not be representative for the mechanism of action of the given treatment. Nevertheless, response to anti-inflammatory agents like minocycline, celecoxib, or omega 3 fatty acids and their superiority over the placebo condition has been shown (eg, Husain et al, Su et al).[23,35,36] Noteworthy, some studies show contradictory results in that no significant difference was found between the treatment and the placebo groups.[37,38] Concluding from this research, anti-inflammatory agents may be a promising approach to treat depression but diverging results on efficacy exist. Thus, the gain over placebo (as single or add-on regimen) and with that the gain for clinical care is somewhat questionable. Despite the ongoing interest and studies on those drugs, they have not been incorporated in treatment guidelines so far. Meta-analyses have been conducted to provide an overview of and to summarize the current evidence from single studies. However, still no definite judgement on usability and a perspective for clinical translation are available.

A possible reason for the lack of applicability of research into clinical practice may lie in the diversity of study designs leading to heterogeneity of effect sizes, especially regarding the inclusion of patients with MDD diagnoses and patients with depressive symptoms. The present work evaluated the current state of research by systematically reviewing the pooled efficacy from meta-analyses and their quality of a variety of sole anti-inflammatory treatments compared to placebo or as add-on to standard care in MDD. Included agents were chosen based on their known direct anti-inflammatory mechanism. Further, the systematic review examines several study characteristics and limiting factors to this research as potential explanations for why it is difficult to obtain consistent and translatable results. With this review, the strength of evidence will be evaluated and thus indicate clinical usability of past research in this field.

Methods

The protocol for this systematic review was designed a priori and registered in PROSPERO under the reference number CRD42022296596. As far as applicable, the review was conducted according to the PRISMA guideline (PRISMA checklist is appended as Supplementary Material).[39]

Eligibility Criteria

Inclusion criteria for human studies were established in PICOS format according to PRISMA: participants – adult patients with a confirmed diagnosis of major depressive disorder as assessed by physician diagnosis, DSM or ICD criteria, or diagnostic interview; intervention – at least one of the following anti-inflammatory drugs as single or add-on agent: minocycline, non-steroidal anti-inflammatory drugs (NSAID), omega 3 fatty acids, anti-TNF, N-acetylcysteine; comparator – placebo, or active comparator such as treatment as usual (TAU) or antidepressants, or TAU/antidepressants plus placebo, corresponding to the intervention setup; outcome – validated depression rating scale; study design – meta-analysis of at least two randomized controlled trials (RCTs) with pooled effect estimates.[39] In case a meta-analysis only included a subset of eligible patients, the meta-analysis was included if a subset analyses on eligible patients was performed and reported. Further, only meta-analyses in English language were included. Exclusion criteria were as follows: 1) patients with otherwise diagnosed depressive episodes, eg, bipolar depression; 2) children and adolescents; 3) classification of depression only by rating scales; 4) other anti-inflammatory agents; 5) meta-analyses including quasi-experimental or observational studies.

Search Strategy

A systematic search was conducted in the databases PubMed/MEDLINE, PsychINFO, Cochrane Library, and Web of Science from inception up until November 2021. Two of the authors conducted the search independently where databases were last consulted by MSS on November 1, 2021, and last consulted by GAH on November 14, 2021. The following search terms were used: ((“depression” [Title/Abstract] OR “depressed”[Title/Abstract] OR “depressive” [Title/Abstract]) AND (“response” [Title/Abstract] OR “effect” [Title/Abstract] OR “efficacy” [Title/Abstract] OR “therapy” [Title/Abstract] OR “treatment” [Title/Abstract]) AND (“anti inflammatory” [Title/Abstract] OR “NSAID” [Title/Abstract] OR “non steroidal anti inflammatory drugs” [Title/Abstract] OR “ASA” [Title/Abstract] OR “acetylsalicylic acid” [Title/Abstract] OR “ASS” [Title/Abstract] OR “aspirin” [Title/Abstract] OR “cox 2 inhibitor” [Title/Abstract] OR “celecoxib” [Title/Abstract] OR “ibuprophen” [Title/Abstract] OR “minocycline” [Title/Abstract] OR “infliximab” [Title/Abstract] OR “anti tnf” [Title/Abstract] OR “omega” [Title/Abstract] OR “NAC” [Title/Abstract] OR “acetylcysteine” [Title/Abstract]) AND (meta-analysis[Publication Type] OR meta analysis[Publication Type])) NOT (“children” [Title/Abstract] OR “adolescent” [Title/Abstract]). Rather broad terms were chosen in order to increase the likelihood of identifying all relevant studies. The search term was entered into Pubmed/Medline as shown previously. For the search in Web of Science ‘Publication Type’ was exchanged for ‘Title’ or ‘Abstract’ and in PsychInfo ‘Publication Type’ was exchanged for ‘Document Type’, and, the search was carried out twice with ‘Title’ and ‘Abstract’ separately for both databases. For the search in Cochrane library, ‘Title/Abstract’ was exchanged for ‘Title Abstract Keyword’.

Selection Process

Two independent reviewers (MSS and GAH) screened the records by title and abstract resulting from database search. Full articles were assessed for eligibility for all remaining records after screening, as well as records where title and abstract were not sufficient to identify non-eligibility. Upon selection differences between the two reviewers, a second screening of the article was conducted, and discrepancies were resolved by consensus.

Data Collection Process and Data Items

The data of interest were obtained by MSS from the eligible records using a data extraction form. Data were retrieved from the full article and the Supplementary Material. If not stated in the article or Supplementary Material, data were obtained from the single studies that were included in the meta-analyses. Extracted data were confirmed by double extraction.

The primary data items of interest were efficacy outcome measures for therapy. This includes pooled effect estimates for mean differences in validated depression rating scales, pooled effect estimates for response and remission rates obtained from validated depression rating scales, and the respective p-values and 95% confidence intervals. Further, the number of studies included in the meta-analysis and I^2 index for heterogeneity were extracted. Heterogeneity is classified according to the Cochrane handbook: 0% to 40% negligible heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity, 75% to 100% considerable heterogeneity.[40] In case the I^2 statistic was not given, Q-statistic and the corresponding p-value were extracted. If a meta-analysis included a study more than once due to multiple intervention arms, each separately included arm was counted as one study. For description of characteristics of the meta-analyses, the composition of populations included in the single studies, the intervention and comparator regimen, the total number of subjects analyzed under the intervention in the meta-analysis, the type of rating scales pooled, and the study design were extracted. In case the number of analyzed subjects was not reported, the number of randomized subjects was used.

Quality Assessment

The quality of included meta-analyses was assessed using the Revised Assessment of Multiple Systematic Reviews tool by MSS (R-AMSTAR).[41] The template to conduct the rating was provided by PEROSH OSH Evidence Group.[42] The R-AMSTAR has the benefit of providing a score between 1 and 4 in several items relevant to risk of bias as assessed by the strength of methodology and the reporting of crucial aspects. By calculating the sum score, a quantitative measure can be derived, allowing the comparison of the quality of meta-analysis with each other in relation to the maximum possible score of 44 points. However, no classification has been established of which value is considered low, medium, or high quality yet. The following aspects are covered by 11 items: provision of an a priori design, selection and extraction by at least two reviewers, methods of literature search, restrictions to publication type and language, traceability of included and excluded studies, provision of study characteristics, assessment of study quality, consideration of study quality for conclusions, appropriateness of study combination methods, assessment of publication bias, and assessment of conflicts of interest.[41] The quality assessment was double checked.

Effect Measures

No restrictions were set to the effect measures used in the meta-analyses. The main outcomes of interest were the mean differences in depressive symptoms (continuous variable) and the comparison of response and remissions rates (dichotomous variables) between the intervention and the control group, as measured by a validated rating scale. Thus, effect estimates can include standard mean difference (SMD), pooled mean difference (MD), weighted mean differences (WMD), Hedges' g, or others if available for mean differences in depressive symptoms. Effect estimates for response and remission rates can include risk ratio (RR), odds ratio (OR), or others if available for response and remission rates.

Synthesis Methods

Since the present work is a systematic review, data were structured to provide a summary and an overview of available data. For presentation of characteristics and results of meta-analyses, data were grouped and tabulated per each intervention type and meta-analyses were sorted by publication date within. If a meta-analysis provided multiple effect measures, the mean differences were listed first, and the response and remission rates were listed second. Regarding the characteristics, ranges of analyzed patients in the intervention group, ranges of publication years, number of studies with comorbid diagnoses or special characteristics of the patient population, and number of studies with monotherapy and/or add-on regimen were evaluated. Regarding the results of the meta-analyses, ranges of effect estimates and heterogeneity indices were evaluated per intervention type to give an impression of the consistency of findings. Further, single studies in the respective meta-analyses were listed to explore the overlap and diversity of studies used to calculate the effect measures. For graphical presentation of the quality assessment, the relative frequencies (percentage) of studies that were rated by each point category for each item were calculated and output as stacked bar graph. This was done using IBM SPSS Statistics for Mac OS version 28.0. For graphical presentation of Forrest plots R studio version 4.0.3 was used.

Results

Search Results

Initially, n=254 studies were retrieved from the databases of which n=20 studies finally met the eligibility criteria. The main reason for exclusion during eligibility assessment was the presence of not purely diagnosed MDD samples. For more details on the selection process see Figure 1 according to the PRISMA guideline.[39] The included studies are listed in Table 1. With respect to the

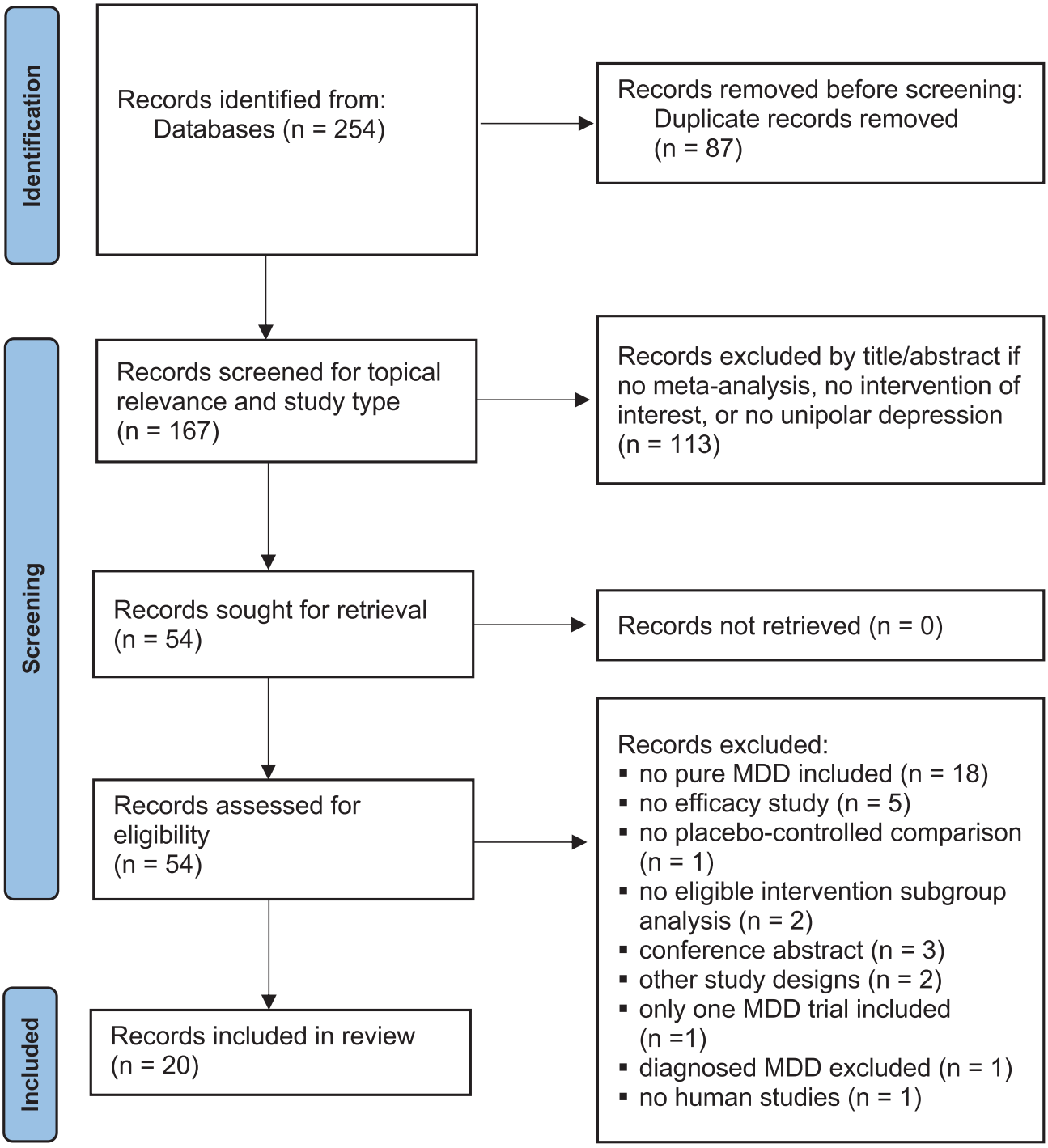

Figure 1 PRISMA 2020 flow diagram of the study selection process.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Creative Commons.[39]
Abbreviations: n, number of studies; MDD, major depressive disorder.

agents of interest, n=5 studies reported on minocycline, n=7 studies reported on NSAIDs (celecoxib), n=14 studies reported on omega 3 fatty acids, n=1 study reported on multiple agents (celecoxib and anti-TNF), and n=0 studies reported on NAC. A list of seriously considered studies that were excluded can be found in Supplementary Table 1.

Study Characteristics

Characteristics of the included meta-analyses are displayed in Table 1. All meta-analyses included RCTs only. Per agent of interest between n=39 and n=82 patients in the minocycline intervention group were pooled, between n=50 and n=160 patients in the celecoxib treatment group were pooled, between n=62 and n=727 patients in the omega 3 fatty acid treatment group were pooled, and n=98 patients in the multiple treatment group were pooled in the meta-analyses. Meta-analyses were conducted between the years 2018 and 2021 for minocycline, from 2014 to 2021 for celecoxib, from 2012 to 2021 for omega 3 fatty acids, and the multiple agents meta-analysis was conducted in 2014. Minocycline meta-analyses included studies using HAMD and MADRS as outcome measure. For celecoxib, only studies using HAMD were pooled in the meta-analyses. Meta-analyses investigating omega 3 fatty acids included a higher variability of outcome measures: HAMD, MADRS, BDI or BDI-II, EPDS, GDS, and IDS-SR. Regarding the patient population, four out of five meta-analyses on minocycline included one study with patients with comorbid HIV, while six out of seven meta-analyses on celecoxib included one study with only female patients. For meta-analyses on omega 3 fatty acids, included populations are more heterogeneous with regard to comorbid diagnoses or special population characteristics and the number of studies with such samples. The following comorbid diagnoses or characteristics were found: coronary heart disease, diabetes, Parkinson's disease, Multiple sclerosis, renal disease, only perinatal women, only elderly women. Only two meta-analyses did not report the inclusion of studies with comorbid patient samples. Lastly, meta-analyses included studies with monotherapy or add-on design. For minocycline, two meta-analyses investigated monotherapy and three meta-analyses included studies of both designs. For celecoxib, all studies used an add-on to antidepressants design. For omega 3 fatty acids, one meta-analysis investigated monotherapy, four investigated add-on to antidepressant therapy only, and nine meta-analyses included studies of both designs.

Quality Assessment

18 studies were assessed for quality. Two studies could not be assessed because they were selected re-analyses of a previously conducted study by other authors and thus did not provide a full methods and results section as usual.[53,54] The R-AMSTAR assessment yielded variable quality of meta-analyses which ranged from 26 to 39 out of 44 possible points. Noteworthy, if no criteria are fulfilled in one category, it is rated with 1 point. Thus, the minimum total score is 11 points. The total scores and the quality rating conducted in the meta-analyses for the single studies are presented in Table 2. Supplementary Table 2 shows the item-based scores. Domains that were generally well reported were duplicate data extraction, methods of literature search, quality assessment, and investigation of heterogeneity and publication bias (see total scores per item in Supplementary Table 2). The domains generally not well reported were provision of a protocol, publication type, retracing excluded studies, study characteristics, and especially consideration of quality assessment in the conclusions (see total scores per item in Supplementary Table 2). Important to note is that in 50% of the meta-analyses, a lack of reporting on consideration of quality assessment in the conclusions (item 8) was present. Figure 2 provides a visual overview of study quality by R-AMSTAR domain. The quality assessment in the meta-analyses of the included studies ranged from very low to high and was thus highly variable despite overlap of included studies.

Results of Meta-Analyses

Minocycline

Details on the results are displayed in Table 3. Three meta-analyses showed superiority of minocycline over the placebo condition for mean difference (SMD ranging between −0.78 and −0.87), while one of them reached significance only when all three studies were included. Those meta-analyses yielded substantial heterogeneity between 53% and 63%. Two studies showed no significant difference with an SMD of −0.81 also with substantial heterogeneity (75% and 77%). One meta-analysis demonstrated superiority of minocycline using response rates by showing that the risk of becoming a responder is 2.83 times higher under exposure to minocycline than becoming a responder under placebo condition,

Table 1 Study Characteristics of the Included Meta-Analyses

Study	Population	Treatment	Comparator	N with Treatment[a]	Outcome Measures	RCT Only
Minocycline						
Rosenblat et al, 2018[43]	MDD, one study with comorbid HIV	Monotherapy minocycline or TAU + minocycline 200mg/day	Placebo or TAU + placebo	80	HAMD MADRS	Yes
Zheng et al, 2019[44]	MDD	TAU + minocycline 200mg/day	TAU + placebo	57	HAMD MADRS	Yes
Köhler-Forsberg et al, 2019[45]	MDD, one study with comorbid HIV	TAU + minocycline 200mg/day	TAU + placebo	52	HAMD MADRS	Yes
Bai et al, 2020[46]	MDD, one study with comorbid HIV	Monotherapy minocycline or TAU + minocycline 200mg/day	Placebo or TAU + placebo	82	HAMD MADRS	Yes
Hang et al, 2021[47]	MDD, one study with comorbid HIV	Monotherapy minocycline or TAU + minocycline 200mg/day	Placebo or TAU + placebo	39	HAMD	Yes
Celecoxib						
Faridhosseini et al, 2014[48]	MDD, one study only females	Antidepressants + celecoxib 200mg/day or 400mg/day	Antidepressants + placebo	160	HAMD	Yes
Na et al, 2014[49]/ Na et al, 2016[50]	MDD, one study only females	Antidepressants + celecoxib 200mg/day or 400mg/day	Antidepressants + placebo	75	HAMD	Yes
Köhler et al, 2014[51]	MDD, one study only females	Antidepressant + celecoxib 200mg/day or 400mg/day	Antidepressants + placebo	68	HAMD	Yes
Köhler-Forsberg et al, 2019[45]	MDD, one study only females	Antidepressant + celecoxib 200mg/day or 400mg/day	Antidepressants + placebo	68	HAMD	Yes
Bai et al, 2020[46]	MDD, one study only females	Antidepressants + celecoxib 400mg/days	Antidepressants + placebo	74	HAMD	Yes
Yuan et al, 2020[52]	MDD	Antidepressant + celecoxib 400mg/days	Antidepressant + placebo	50	HAMD	Yes
Hang et al, 2021[47]	MDD, one study only females	Antidepressant + celecoxib 200mg/day or 400mg/day	Antidepressants + placebo	52	HAMD	Yes
Omega3 fatty acids						
Martins et al, 2012[53] reanalysis	MDD[b], three studies only perinatal women, one study comorbid Parkinson's disease	Monotherapy omega3 or antidepressants + omega3 multiple regimen[e]	Placebo or antidepressants + placebo	265	HAMD MADRS EPDS	Yes
Martins et al, 2012[53] updated analysis	MDD[b,c], three studies only perinatal women, each one study comorbid Parkinson's disease, comorbid coronary heart disease, comorbid diabetes, only elderly women	Monotherapy omega3 or antidepressants + omega3 multiple regimen[f]	Placebo or antidepressants + placebo	612	HAMD MADRS EPDS BDI-II GDS IDS-SR	Yes
Lin et al, 2012[54]	MDD[b], three studies only perinatal women, one study comorbid Parkinson's disease	Monotherapy omega3 or antidepressants + omega3 multiple regimen[g]	Placebo or antidepressants + placebo	254	HAMD BDI MADRS	Yes

(*Continued*)

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Table 1 (Continued).

Study	Population	Treatment	Comparator	N with Treatment[a]	Outcome Measures	RCT Only
Grosso et al, 2014[55]	MDD[c,d], three studies only elderly women	Monotherapy omega3 or antidepressants + omega3 multiple regimen[h]	Placebo or antidepressants + placebo	229	HAMD MADRS GDS BDI-II	Yes
Appleton et al, 2015[56]	MDD[c], one study each with comorbid diabetes, coronary heart disease, Parkinson's disease, renal disease, one study only elderly women	Monotherapy omega3 or antidepressants + omega3 multiple regimen[k]	Placebo or antidepressants + placebo	727	HAMD MADRS GDS BDI-II	Yes
Mocking et al, 2016[57]	MDD, one study each with comorbid coronary heart disease and diabetes	Monotherapy omega3 or antidepressants + omega3 multiple regimen[j]	Placebo or antidepressants + placebo	595	HAMD, MADRS	Yes
Sarris et al, 2016[58]	MDD, one study with comorbid diabetes	Antidepressants + omega3 multiple regimen[l]	Antidepressants + placebo	226	HAMD BDI-II MADRS	Yes
Wei-Hong et al, 2017[59]	MDD (how diagnosis was obtained not clear)	Monotherapy omega3 multiple regimen[i]	Placebo	62	HAMD	Yes
Schefft et al, 2017[60]	MDD, one study each with comorbid diabetes, coronary heart disease, Parkinson's disease, Multiple sclerosis	Antidepressants + omega3 multiple regimen[m]	Antidepressants + placebo	212	HAMD BDI MADRS	Yes
Bai et al, 2020[46]	MDD[b,c], three studies perinatal women, one study each with Parkinson's disease, coronary heart disease, diabetes, Multiple sclerosis, one study only elderly women	Monotherapy omega3 or TAU/sertraline + omega3 multiple regimen[n]	Placebo or TAU/sertraline + placebo	603	HAMD EPDS MADRS BDI-II GDS	Yes
Luo et al, 2020[61]	MDD	Monotherapy omega3 or antidepressants + omega3 multiple regimen[o]	Placebo or antidepressants + placebo	493	HAMD MADRS IDS-SR	Yes
Jeremiah et al, 2020[62]	MDD	Antidepressants + omega3 multiple regimen[p]	Antidepressants + placebo	160	HAMD BDI	Yes

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Hang et al, 2021[47]	MDD, two studies with comorbid coronary heart disease, one study each with Multiple sclerosis and Parkinson's disease	Monotherapy omega3 or antidepressants/ TAU + omega3 multiple regimen[q]	Placebo or antidepressants/ TAU + placebo	406	BDI-II HAMD MADRS	Yes
Chambergo-Michilot et al, 2021[63]	MDD, two studies with coronary heart disease	Sertraline + omega3 multiple regimen[r]	Sertraline + placebo	133	HAMD	Yes
Chambergo-Michilot et al, 2021[63]	MDD, two studies with coronary heart disease	Sertraline + omega3 multiple regimen[r]	Sertraline + placebo	158	BDI	Yes
Multiple agents						
Köhler et al, 2014[51]	MDD, one study only females	Antidepressants + celecoxib and monotherapy infliximab or TAU + infliximab multiple regimen[s]	Placebo or antidepressants/ TAU + placebo	98	HAMD	Yes

Notes: [a]Analyzed if available, otherwise randomized. [b]One study included patients with dysthymia since MDD was defined this way by the authors (Rees et al, 2008). [c]One study included patients with dysthymia since MDD was defined this way by the authors (Rondanelli et al, 2010). [d]One study included patients with dysthymia since MDD was defined this way by the authors (Rondanelli et al, 2011). [e]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 1.1g/day +DHA 0.8g/day; DHA 1.6g/day+EPA 0.4g/day; EPA 2.2g/day+DHA 1.2g/day; EPA 1g/day; EPA 1g/day / EPA 2g/day / EPA 4g/day; DHA 2.4g/day+EPA 0.6g/day; DHA 2.2g/day+EPA 0.6g/day; EPA 0.72g/day+DHA 0.48g/day. [f]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 1.1g/day+DHA 0.8g/day; DHA 1.6g/day+EPA 0.4g/day; EPA 2.2g/day+DHA 1.2g/day; EPA 930mg/day+DHA 750mg/day; EPA 1g/day; EPA 1.67g/day+DHA0.83g/day; EPA 0.9g/day; EPA 1g/day / EPA 2g/day / EPA 4g/day; DHA 2.4g/day+EPA 0.6g/day; DHA 2.2g/day+EPA 0.6g/day; EPA 0.72g/day+DHA 0.48g/day; EPA 1g/day; EPA 1.05g/day+DHA 0.15g/day. [g]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 1.1g/day+DHA 0.8g/day; DHA 1.6g/day+EPA 0.4g/day; EPA 2.2g/day+DHA 1.2g/day; EPA 1 g/day; EPA 1g/day / EPA 2g/day / EPA 4g/day; DHA 2.4g/day+EPA 0.6g/day; DHA 2.2g/day+EPA 0.6g/day; EPA 0.72g/day+DHA 0.48g/day; EPA 1.05g/day+DHA0.15g/day. [h]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 1g/day; EPA 1.67g/day+DHA 0.83g/day; DHA 2.2g/day+EPA 0.6g/day; EPA 1g/day; EPA 1.05g/day+DHA 0.15g/day; EPA 1.8g/day+DHA 0.4g/day; EPA 1.67g/day+DHA 0.83g/day; EPA+DHA 2.5g/day. [i]EPA 1.1g/day+DHA 0.8g/day; DHA 1.6g/day+EPA 0.4g/day; EPA 2.2 g/day+DHA 1.2g/day. [j]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 930mg/day+DHA 750mg/day; EPA 1g/day; EPA 0.9g/day; EPA 1.06g/day+DHA 0.274g/day; EPA 0.18g/day+DHA 0.9g/day; DHA 1g/ / EPA 1g/day; DHA 2.2g/day+EPA 0.6g/day; EPA 1g/day; EPA 1.05g/day+DHA 0.15g/day; EPA 1.05g/day+DHA 0.15g/day; EPA 1.8g/day+DHA 0.4g/day. [k]EPA 0.9g/day; EPA 930mg/day+DHA 750mg/day; EPA 0.72g/day+DHA 0.48g/day; EPA 1.8g/day+DHA 0.4g/day; DHA 2.2g/day+EPA 0.6g/day; EPA 1g/day; EPA 1.05g/day+DHA 0.15g/day; EPA 1.05g/day+DHA 0.15g/day; DHA 2g/day; EPA 1.06g/day+DHA 0.274g/day / EPA 0.18g/day+DHA 0.9g/day; EPA 1g/day; EPA 2g/day; EPA 1g/day / EPA 2g/day / EPA 4g/day; EPA 1.67g/day+DHA 0.83g/day; DHA 2.4g/day+EPA 0.6g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 740mg/d+DHA 400mg/d / EPA 1480 mg/d+ DHA 800 mg/d; EPA 1080mg/d+DHA 720mg/d; EPA 3g/day; EPA 3420mg/d+DHA 1800 mg/d. [l]EPA 4.4g/day+DHA 2.2g/day; EPA 930mg/day+DHA 750mg/day; EPA 1.8g/day+DHA 0.4g/day; EPA 1g/day / DHA 1g/day; EPA 2g/day; EPA 1g/day / 2g/day / 4g/day; EPA 1g/day; EPA 0.9g/day. [m]DHA 1g/day / EPA 1g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 1.95g/day+DHA 1.35g/day; EPA 1.8g/day+DHA 0.4g/day; EPA 930mg/day+DHA 750mg/day; EPA 1.14g/day+DHA 0.6 g/day; EPA 1g/day; EPA 2g/day; EPA 0.9g/day; EPA 0.72g/day+DHA 0.48g/day. [n]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; EPA 1.1g/day+DHA 0.8g/day; DHA 1.6g/day+EPA 0.4g/day; EPA 2.2g/day+DHA 1.2g/day; EPA 930mg/day+DHA 750mg/day; EPA 1g/day; EPA 1.67g/day+DHA0.83g/day; EPA 0.9g/day; EPA 1.06g/day+DHA 0.274g/day; EPA 0.18g/day+DHA 0.9g/day; EPA 1.06g/day+DHA0.26g/day; EPA 0.18g/day+DHA0.9g/day. [o]EPA 2g/day; DHA 2g/day; EPA 4.4g/day+DHA 2.2g/day; DHA 2,2g/day+EPA 0.6g/day; EPA 1g/day; EPA 1.05g/day+DHA 0.15g/day; DHA 1g/day / EPA 1g/day; EPA 1.06g/day+DHA 0.274g/day / EPA 0.18g/day+DHA 0.9g/day; EPA 1.8g/day+DHA 0.4g/day. [p]EPA 1.8g/day+DHA 0.4g/day; omega3 1g/day; EPA 1g/day; DHA 1g/day / EPA 1g/day; EPA 2g/day; EPA 1g/day / 2g/day / 4g/day. [q]EPA 930mg/day+DHA 750mg/day; EPA 2g/day; EPA 1.8g/day+DHA 0.4g/day; EPA 1g/day; DHA 2g/day; EPA 1g/day; EPA 1.06g/day+DHA 0.274g/day / EPA 0.18g/day+DHA 0.9g/day; EPA 2g/day; EPA 1.06g/day+DHA 0.26g/day / EPA 0.18g/day+DHA 0.9g/day; EPA 1.95g/day+DHA 1.35g/day; EPA 0.72g/day+DHA 0.48g/day. [r]EPA 930mg/day+DHA 750mg/day; omega3 1g/day; omega3 1g/day; EPA 2g/day. [s]celecoxib 200mg/day / 400mg/day; infliximab 5mg/kg.

Abbreviations: MDD, major depressive disorder; HIV, human immunodeficiency virus; TAU, treatment as usual; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; EPDS, Edinburgh Postnatal Depression Scale; BDI, Beck Depression Inventory; GDS, Geriatric Depression Scale; IDS-SR, Inventory of Depressive Symptomatology self-rating; RCT, randomized controlled trial.

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Table 2 R-AMSTAR Quality Rating of Meta-Analyses Ranked in Descending Order and Quality Ratings by the Meta-Analyses of the Included Single Studies

Study	R-AMSTAR Total Score (Max. Score 44)	Overall Quality Estimation of Single Studies in Meta-Analyses
Appleton et al, 2015[56]	39	Very low to low
Chambergo-Michilot et al, 2021[63]	36	Moderate to high
Hang et al, 2021[47]	34	Moderate to high
Mocking et al, 2016[57]	33	High
Zheng et al, 2019[44]	35, corrected 33[a]	Moderate to high
Faridhosseini et al, 2014[48]	32	Moderate to high
Bai et al, 2020[46]	31	Moderate to high
Grosso et al, 2014[55]	31	Range from 4–13 points out of 13 points
Jeremiah et al, 2020[62]	31	Low to moderate
Rosenblat et al, 2018[43]	31	Low
Köhler-Forsberg et al, 2019[45]	30	Low
Wei-Hong et al, 2017[59]	30	High
Yuan et al, 2020[52]	33, corrected 30[b]	High, but only assessed for non-randomized studies which were not studies of interest for this meta-analysis
Na et al, 2014[49]	29	Low to high
Köhler et al, 2014[51]	28	Low
Luo et al, 2020[61]	28	Moderate
Schefft et al, 2017[60]	27	Moderate to high
Sarris et al, 2016[58]	26	Was not assessed
Lin et al, 2012[54]	Not assessable – letter to the editor with selected reanalysis	
Martins et al, 2012[53]	Not fully assessable – selected reanalysis	

Notes: Quality assessment was judged based on what authors reported in the manuscript and Supplemental Material. [a]Publication bias was considered and analyzed but not for the major depression sample that is of interest for this review (only N=2 studies). Thus, two points must be subtracted when only accounting for the major depressed sample. [b]Points for scientific quality items were only rated for non-randomized studies that were not studies of interest for this review. Thus, three points must be subtracted when only accounting for randomized controlled trials.

without heterogeneity. The reported meta-analyses are based on two to three studies and have a high overlap in those (see Supplementary Table 3A).

Celecoxib

All meta-analyses demonstrated superiority of celecoxib over placebo. SMD ranged between −0.82 and 3.43 for mean difference, signs depending on the calculation method. One study calculated WMD of 3.26. Those meta-analyses yielded none or low heterogeneity of 0% or 33%. Six meta-analyses calculated pooled response rates, also resulting in superiority of celecoxib. As for risk ratios, the risk of becoming a responder is 1.55 or 1.88 times higher under exposure to celecoxib than becoming a responder under placebo condition. As for odds ratios, responders have between 6.49 and 9.23 times higher risk of having been exposed to celecoxib as compared to the placebo condition. Heterogeneity of studies was not present. Five meta-analyses calculated pooled remission rates, again resulting in superiority of celecoxib. As for risk ratio, the risk of becoming a remitter is 4.11 times higher under exposure to celecoxib than becoming a responder under placebo condition. As for odds ratios, remitters have between 6.47 and 7.89 times higher risk of having been exposed to celecoxib as compared to the placebo condition. No heterogeneity was present. Details on the results for celecoxib are displayed in Table 3. The reported meta-analyses are based on three to four studies and thus have a high overlap in those (see Supplementary Table 3B).

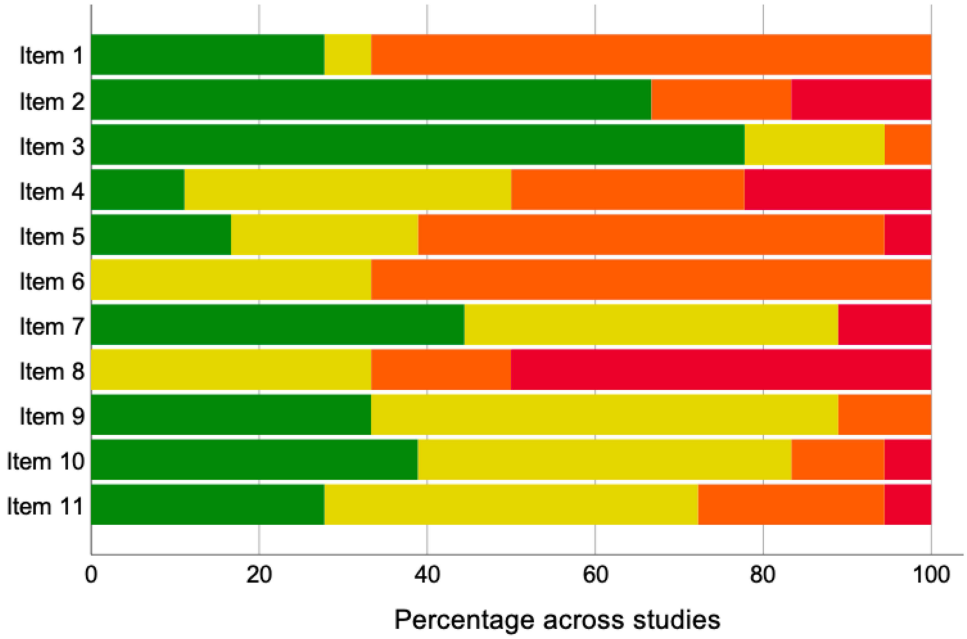


Figure 2 Quality of included meta-analysis by R-AMSTAR domain.
Notes: Per item, the relative frequencies (percentage) of studies that were rated by the respective point category is displayed; green represents 4 points, yellow represents three points, orange represents two points, red represents one point. The corrected scores were considered.

Omega 3 Fatty Acids

Twelve meta-analyses demonstrated superiority of omega 3 fatty acids over placebo. SMD ranged between −0.91 and 1.243 for mean difference, signs depending on the calculation method, and one meta-analysis calculated Hedges' g of 0.608. Those meta-analyses yielded none to substantial heterogeneity between 0% and 87.4%. One study with two meta-analyses did not show superiority of omega 3 fatty acids for mean difference (pooled MD of 0.42 and SMD of 0.50). Heterogeneity was found to be moderate at 35.7% and considerable at 94.1%. Two meta-analyses calculated pooled response rates, not demonstrating superiority of omega 3 fatty acids. Here, heterogeneity of 6% and 30% was low. One meta-analysis calculated pooled remission rates, also not showing superiority of omega 3 fatty acids and a low heterogeneity of 7%. Details on the results are displayed in Table 3. The reported meta-analyses are based on 2 to 25 studies resulting in a low to moderate overlap (see Supplementary Tables 3C.1–3C.3). This seems a specialty of the omega 3 fatty acids meta-analyses at least partly due to a higher variety in populations of interest (see section study characteristics).

Table 3 Parameters Extracted from the Meta-Analyses Indicative of Pooled Efficacy of Anti-Inflammatory Agents

Study	Number of Studies Included[a]	Effect Size Mean Difference / Response Yes-No	p	95% CI	Heterogeneity
Minocycline					
Rosenblat et al, 2018[43]	3	SMD = −0.78	0.005	[−1.33;-0.24]	I^2 = 62%
Zheng et al, 2019[44]	2	SMD = −0.81	0.08	[−1.73;0.10]	I^2 = 75%
Köhler-Forsberg et al, 2019[45]	2[b]	SMD = −0.81	0.08	[−1.72;0.10]	I^2 = 77%
	3[c]	SMD = −0.87	0.003	[−1.45;-0.29]	I^2 = 63%
Bai et al, 2020[46]	3	SMD = −0.79	0.002	[−1.29;-0.28]	I^2 = 53%
Hang et al, 2021[47]	2	RR = 2.83 response rates	0.02	[1.14;6.98]	I^2 = 0%

(*Continued*)

Table 3 (Continued).

Study	Number of Studies Included[a]	Effect Size Mean Difference / Response Yes-No	p	95% CI	Heterogeneity
Celecoxib					
Faridhosseini et al, 2014[48]	3	SMD = 3.3 (week 4)	0.002	[1.2;5.3]	I^2 = 33%
		SMD = 3.43 (week 6)	<0.001	[1.9;4.9]	I^2 = 0%
Faridhosseini et al, 2014[48]	3	OR = 6.6 response rates	<0.001	[2.5;17]	I^2 = 0%
Faridhosseini et al, 2014[48]	4	OR = 6.6 remission rates	<0.001	[2.7;15.9]	I^2 = 0%
Na et al, 2014[49]/ Na et al, 2016[50]	4	WMD = 3.26	<0.001	[1.81;4.71]	I^2 = 0%
Na et al, 2014[49]	4	OR = 6.49 response rates	<0.001	[2.89;14.55]	I^2 = 0%
Na et al, 2014[49]	4	OR = 6.58 remission rates	<0.001	[2.55;17.00]	I^2 = 0%
Köhler et al, 2014[51]	4	SMD = −0.82	<0.001	[−1.17;-0.46]	I^2 = 0%
Köhler et al, 2014[51]	3	OR = 6.59 response rates	<0.001	[2.24;19.42]	I^2 = 0%
Köhler et al, 2014[51]	4	OR = 7.89 remission rates	<0.001	[2.94;21.17]	I^2 = 0%
Köhler-Forsberg et al, 2019[45]	4	SMD = −0.82	<0.001	[−1.17;-0.46]	I^2 = 0%
Köhler-Forsberg et al, 2019[45]	4	RR = 1.88 response rates	<0.001	[1.45;2.45]	I^2 = 0%
Köhler-Forsberg et al, 2019[45]	4	RR = 4.11 remission rates	<0.001	[1.86;9.11]	I^2 = 0%
Bai et al, 2020[46]	4	SMD = −0.76	<0.001	[−1.14;-0.39]	I^2 = 0%
Yuan et al, 2020[52]	3	OR = 9.23 response rates	<0.001	[3.07;27.75]	I^2 = 0%
Yuan et al, 2020[52]	3	OR = 6.47 remission rates	0.003	[1.88;22.29]	I^2 = 0%
Hang et al, 2021[47]	3	RR = 1.55 response rates	<0.001	[1.23;1.95]	I^2 = 0%
Omega3 fatty acids					
Martins et al, 2012[53] reanalysis	11[d]	SMD = 0.242	0.014	[0.048;0.436]	Q = 38.135 p < 0.001
Martins et al, 2012[53] updated analysis	16[d]	SMD = 0.363	0.005	[0.120;0.605]	Q = 55.293 p < 0.001
Lin et al, 2012[54]	12	SMD = 0.23	0.01	[0.05;0.42]	I^2 = 73%
Grosso et al, 2014[55]	12	SMD = 0.560	0.002	[0.20;0.92]	I^2 = 71%
Appleton et al, 2015[56]	25	SMD = −0.30	0.003	[−0.50;-0.10]	I^2 = 59%
Appleton et al, 2015[56]	15	OR = 1.39 response rates	0.09	[0.905;2.04]	I^2 = 6%
Appleton et al, 2015[56]	6	OR = 1.38 remission rates	0.17	[0.87;2.20]	I^2 = 7%
Mocking et al, 2016[57]	13	SMD = 0.398	0.006	[0.114;0.682]	I^2 = 73.36
Sarris et al, 2016[58]	11	Hedges' g = 0.608	0.009	[0.15;1.06]	I^2 = 82%
Wei-Hong et al, 2017[59]	3	SMD = 0.63	<0.001	[0.27;1.00]	I^2 = 0%
Schefft et al, 2017[60]	10	SMD = −0.48	0.01	[−0.84;-0.11]	I^2 = 64%
Bai et al, 2020[46]	12	SMD = −0.35	0.008	[−0.60;-0.09]	I^2 = 61%
Luo et al, 2020[61]	9[e]	SMD = −0.71[5]	Not stated	[−1.13;−0.28][5]	I^2 = 87.4%
	10[f]	SMD = 1.243[6]		[0.060;2.414][6]	
Jeremiah et al, 2020[62]	9	SMD = −0.91	<0.001	[−1.44;-0.38]	I^2 = 80%
Hang et al, 2021[47]	12	RR = 1.10 response rates	0.33	[0.91;1.34]	I^2 = 30%
Chambergo-Michilot et al, 2021[63]	2[g]	Pooled MD = 0.42	n.s.	[−1.44;2.29]	I^2 = 35.7%
Chambergo-Michilot et al, 2021[63]	3[h]	SMD = 0.50	n.s.	[−0.51;1.50]	I^2 = 94.1%
Multiple agents					
Köhler et al, 2014[51]	5	SMD = −0.54	0.05	[−1.08;-0.01]	I^2 = 68%

Notes: [a]Studies included more than once due to multiple arms counting as multiple studies; [b]considered as MDD by authors; [c]considered as MDD and depressive symptoms, but Emadi-Kouchak et al, 2016 is considered MDD by other authors; [d]likely studies with multiple arms only counted once/paper does not provide appropriate information; [e]as per results section; [f]as per abstract; [g]outcome HAMD; [h]outcome BDI.

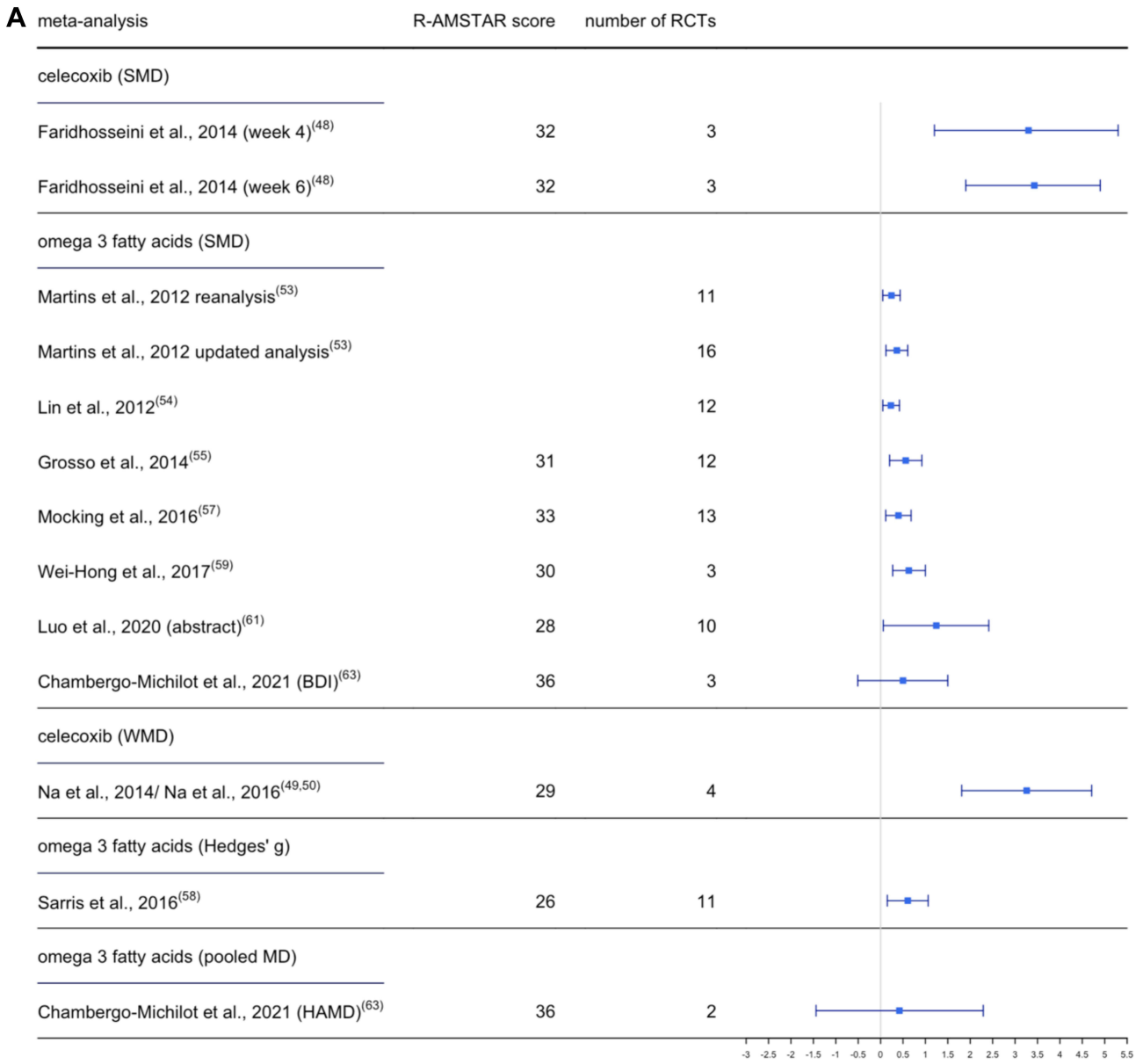
Abbreviations: CI, confidence interval; SMD, standard mean differences; WMD, weighted mean differences; OR, pooled odds ratios; RR, relative risk; pooled MD, pooled mean difference.

Multiple Agents

One meta-analysis included celecoxib and infliximab showing an SMD of −0.54 at the border of significance and substantial heterogeneity of 68%. Details are presented in Table 3. The reported results are based on five studies; a statement on overlap is obsolete (see Supplementary Table 3D).

Overall Overview

Figure 3A and B show a Forrest plot for mean differences to provide an easy to grasp overview of the reviewed data and thus the strength and consistency across meta-analyses. Depending on the calculation method of mean differences, positive and negative values can occur. To avoid misleading interpretation, positive and negative values are displayed as separate figures. Similarly, like for mean differences, Figure 4 shows a Forrest plot for risk ratios and odds ratios, separately for response and remission rates.



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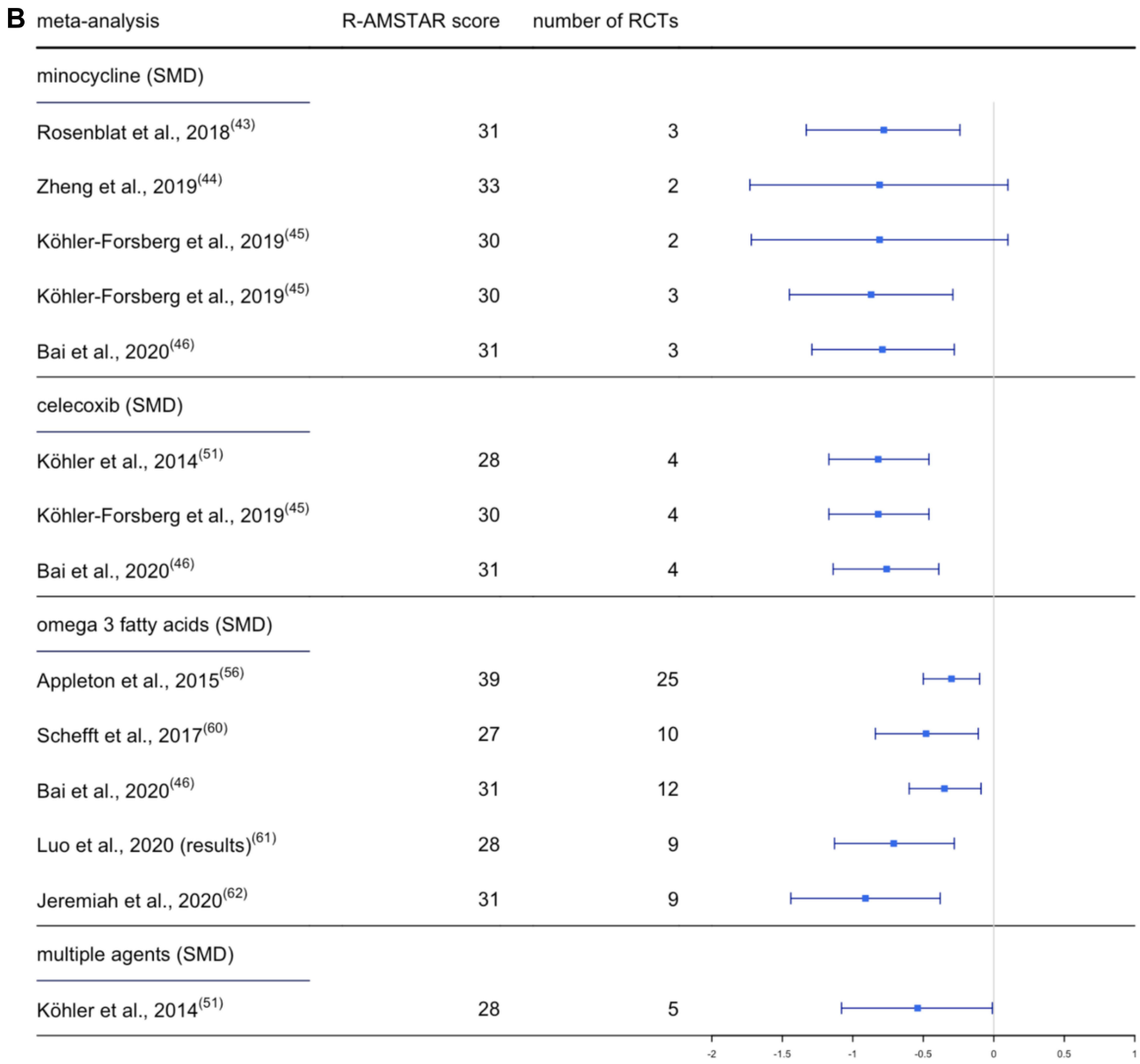

Figure 3 (**A**) Positive mean differences from meta-analyses by agent and effect size parameter. (**B**) Negative mean differences from meta-analyses by agent and effect size parameter.
Abbreviations: RCTs, randomized controlled trials; SMD, standard mean difference; BDI, Beck Depression Inventory; WMD, weighted mean difference; MD, mean difference; HAMD, Hamilton Depression Rating Scale.

Discussion

Summary of Main Findings

In total, 20 meta-analyses were analyzed, some of which provided multiple effect estimates. Investigated agents were minocycline, celecoxib, omega 3 fatty acids, and a combination of celecoxib and infliximab. All meta-analyses included RCTs only. A diversity of characteristics was observed regarding included study populations, sample size, outcome scales, treatment regimen, the variety of dosages for omega 3 fatty acids (different combination or monotherapy of EPA and DHA), and year of publication. Characteristics were quite consistent for meta-analyses on celecoxib, rather consistent for meta-analyses on minocycline, and rather diverse for meta-analyses on omega 3 fatty acids. Noteworthy, only few single studies were available for celecoxib and minocycline which were included in multiple meta-analyses.

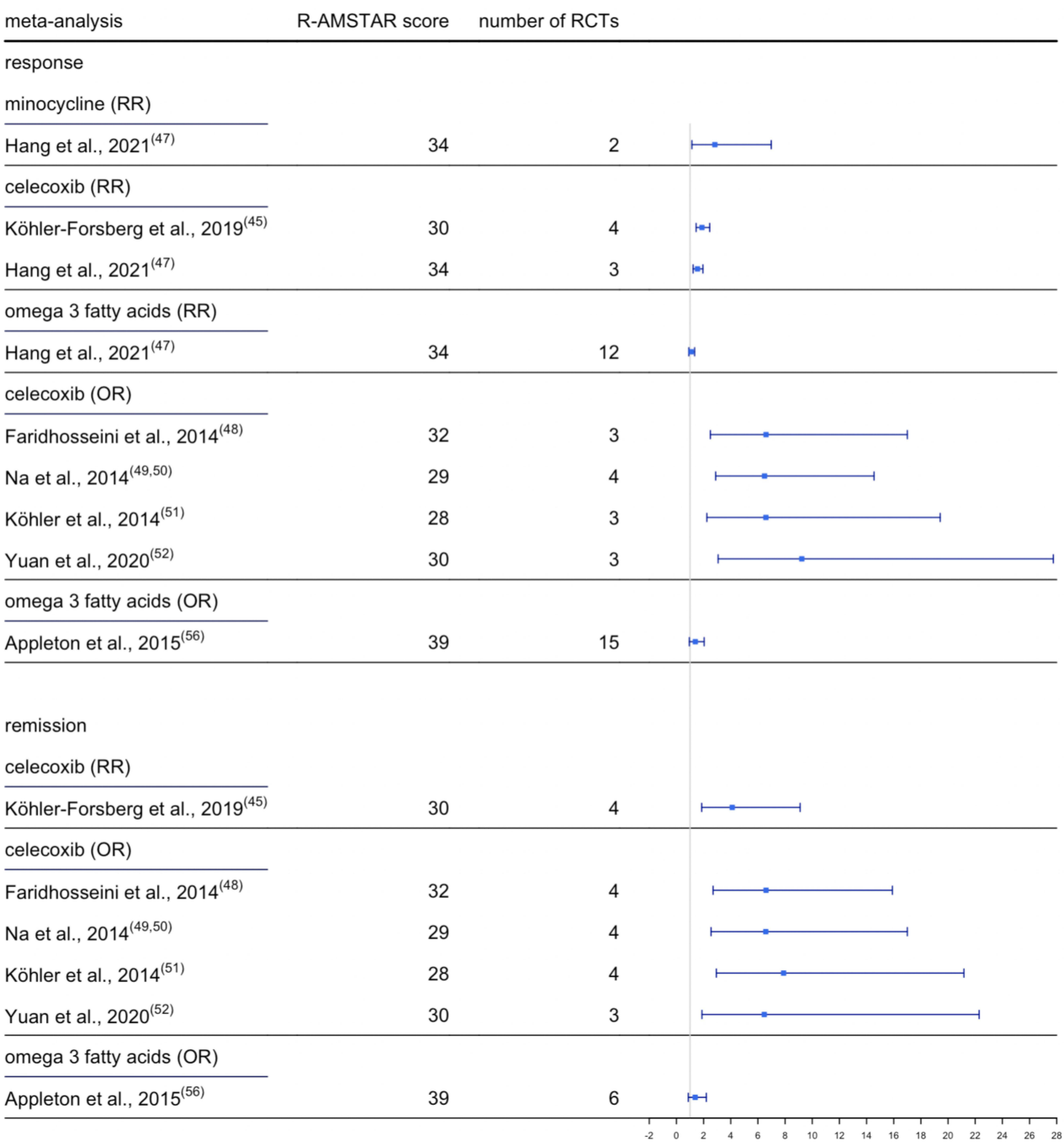

Figure 4 Risk ratios and odds ratios from meta-analyses by agent for response and remission.
Abbreviations: RCTs, randomized controlled trials; RR, risk ratio; OR, odds ratio.

Interpreting results, SMD corresponds to Cohen's d and Hedges' g is the adjusted Cohen's d and thus approximates it.[133,134] Minocycline showed superiority over placebo conditions in three meta-analyses with medium to large effect size in mean difference and substantial heterogeneity in single study effect sizes. Findings on response rates are in accordance with these results. Two meta-analyses with similar effect sizes did not deliver significant superiority of minocycline. Those included only the same two studies and had the highest heterogeneity. In general, a high overlap in studies was present between the meta-analyses, thus leading to high overlap in investigated patient populations. Celecoxib showed superiority over placebo conditions in five meta-analyses with

large and very large effect size in mean difference (at the border of medium to large effect size in one case) and with practically no heterogeneity in single study effect sizes. Effect sizes diverge more than in the minocycline meta-analyses even though a very high overlap in included studies exists also. For response and remission rates a large effect is present as well. Omega 3 fatty acids showed superiority over placebo conditions in twelve meta-analyses with mainly small and medium effect sizes in mean differences, but also a large effect size in two cases, and with substantial heterogeneity and negligible heterogeneity in one case. These effect sizes have a smaller range than for celecoxib but a higher range in heterogeneity. Two meta-analyses with small to medium effect sizes did not deliver significant superiority of omega 3 fatty acids. Those had moderate to considerable heterogeneity and included only two and three studies, respectively. Also, for response and remission rates no significant effects emerged with negligible heterogeneity. In omega 3 fatty acids meta-analyses, much less overlap in included studies was present than in minocycline and celecoxib meta-analyses. Only Martins et al and Lin et al as well as Martins et al and Appleton et al had a rather high overlap in included studies, thus leading to rather high overlap in therapy regimen, sample sizes, patient populations, outcome scales, SMD, and p-values.[53,54,56] In general, the small overlap in included studies may be due to different main research questions in the omega 3 fatty acids meta-analyses. Lastly, the mixed agents study almost showed superiority of anti-inflammatory treatment over placebo with a medium effect size and substantial heterogeneity.

Heterogeneity

Notably, in general when response or remission rates were evaluated, heterogeneity was almost in every case at 0% as compared to much higher heterogeneity for pooled mean differences. This observation was also made by Alba et al.[135] The authors state that one potential explanation for this phenomenon is the precision of included studies in a meta-analysis.[135] As continuous outcomes have more statistical power, they result in narrower confidence intervals.[135] Combining results with narrow confidence intervals can then lead to higher heterogeneity since these confidence intervals may have a smaller overlap and differences in study effects for the I^2 statistic are created. Further, meta-analyses with continuous outcomes seemed to produce higher heterogeneity the more studies were included as opposed to meta-analyses with binary outcomes.[135] Vice versa, with lower precision of study results and a higher confidence interval, heterogeneity is smaller, which appears to be more prevalent in meta-analyses investigating studies with binary outcomes.[135] The celecoxib meta-analysis showed a heterogeneity of 0% independently of a continuous or a binary outcome. This may speak for the strength of the results since single studies seem to produce similar effects. Indeed, for mean differences the confidence intervals were highly overlapping, but also small explaining the highly significant results.[45] The same can be observed for response rates, while a high overlap but also large confidence intervals exist for remission rates.[45] For the minocycline meta-analyses, the described differences in heterogeneity depending on the outcome are present. For mean differences, the confidence intervals are largely overlapping but not as much as in celecoxib studies.[43,45] For response rates, the confidence interval of one study contains the confidence interval of the other study entirely which may explain the low heterogeneity.[47] The omega 3 fatty acids meta-analyses show a similar trend, even though with dichotomous outcomes heterogeneity is larger than 0%. For mean differences, the confidence intervals of single studies vary in range and are less overlapping, while for dichotomous outcomes single studies presented much larger confidence intervals and thus are overlapping to a greater extent.[56] However, variety seems larger than in celecoxib and minocycline studies supporting the idea of Alba et al of higher heterogeneity the more studies are included.[135] This may be attributed to a larger sample size which leads to even smaller confidence intervals and thus less overlap. Indeed, the omega 3 fatty acids meta-analyses included the most studies, thus the largest sample sizes, and have the smallest confidence intervals (see Figures 3A and B and 4). Further, between the omega 3 fatty acids meta-analyses exists higher variety in the number of included studies as compared to minocycline and celecoxib meta-analyses. Noteworthy, it is difficult to compare the statistical indices numerically between the meta-analyses due to different statistical methods which result in different numeric outcome estimates and confidence intervals. Thus, the described observations rather refer to the consistency of patterns noticed within the respective meta-analyses. However, Russo proposes that the statistical methods are less relevant than the determination of combinability of studies prior to statistical testing.[136] In case of critical heterogeneity in study characteristics statistical methods cannot account for erroneous

combination attempts.[136] The analyzed meta-analyses of the present systematic review often did not report sufficiently on defined criteria for data combination (only 6 out of 18 rated meta-analysis fulfilled this criterion on subitem 9A) and a priori testing of heterogeneity guiding this decision.

It is important to note that heterogeneity test results are often misinterpreted.[136] These tests do not validate the similarity of studies to be combined in meta-analysis but test the hypothesis whether effect sizes of single studies are sufficiently equal to guide the decision to calculate a pooled effect estimate.[136] Variability in study characteristics can influence the study's effect size and differences in (the variability of) those characteristics between studies can deliver an explanation for heterogenous effect sizes and the strength of evidence from meta-analysis. In the present work, next to statistical aspects, potential sources of heterogeneity may lie in the study characteristics. In the celecoxib meta-analyses very little diversity of certain characteristics can be observed: same outcome scales were used, add-on studies exclusively, high overlap of single studies included in meta-analyses and thus overlap in included populations. In the minocycline meta-analyses, somewhat higher diversity in characteristics was present: two outcome scales, monotherapy and add-on regimen, but on the other hand, a high overlap of single studies included and thus overlap in included populations. For the omega 3 fatty acids meta-analyses, the highest variability in characteristics was present: multiple outcome scales, monotherapy and add-on regimen, composition of omega 3 treatment with different dosages and different placebo agents, low overlap of single studies included and thus higher variety in included populations.

Diagnostic Misclassification

During the conduct of the present systematic review, some obstacles occurred. First, studies often consider bipolar depression a similar pathology as unipolar depression, while differences in biological underpinnings, especially in immune disturbances, have barely been investigated. Thus, the present work focusses on unipolar depression, exclusively, to provide higher clinical relevance of findings. Many meta-analyses that were excluded throughout the selection process, especially on omega 3 fatty acids, claimed to have investigated MDD patients while the samples from the single studies included mixed diagnoses and some based patient inclusion solely on the score of a depression rating scale (see Supplementary Table 1). Appleton et al and Mocking et al, for example, included studies with diagnosed MDD patients and included an eligible diagnosed MDD subset if samples were mixed with non-diagnosed depressive symptoms (like in the study of Lucas et al).[56,57,114] Much caution is needed to disentangle the diagnostic status of included populations, while the inclusion of an MDD sample is sometimes claimed improvidently. This often makes it necessary to carefully review the eligibility criteria for patients in the single studies included in the meta-analyses. It would be interesting though to compare treatment efficacy of meta-analyses on diagnosed MDD populations versus populations with depressive symptoms as measured by standard rating scales.

Treatment Regimen

A critical aspect is the use of different treatment regimen in add-on studies, which make it difficult to deduce specific treatment recommendations from meta-analytical results. Furthermore, not all meta-analyses provided information on what defined treatment as usual (eg, Rosenblat et al).[43] Additionally, the validity of placebo in the omega 3 fatty acid studies can be questioned since other types of oil may also be defined as an active comparator, at least if an anti-inflammatory mechanism of action cannot be ruled out entirely. Lastly, on meta-analytical level one publication included combined agents of interest.[51] To formulate recommendations for treatment, this approach seems rather counterproductive because it again does not provide specific information.

Outcomes

A problem with combining different rating scales in one meta-analysis arises from their differences in sensitivity to changing symptoms, which in turn questions the comparability of changes in symptom scores. Another considerable aspect is the choice of values for continuous outcomes which has been discussed by Andrade.[137] Some studies assess the endpoint values as efficacy outcome, which can only be positive values, and some studies assess the score change from baseline to endpoint, which can be positive or negative values depending on how the difference was calculated and whether values increased or decreased.[137] Different outcome values must be interpreted differently, and pooled effect

sizes are thus difficult to compare between meta-analyses and should not be pooled in one meta-analysis in general. The presented meta-analyses often analyzed the score change (eg, Bai et al, Köhler-Forsberg et al).[45,46] Some of them analyzed the endpoint score (eg, Zheng et al, Jeremiah et al).[44,62] Further, the choice of outcome values may not be stated, so it is not possible to judge comparability appropriately (eg, Wei-Hong et al).[59] All meta-analyses on mean differences for celecoxib used the score change which strengthens the comparability of effect sizes and conclusions drawn from these investigations.

Quality Assessment

Summarizing findings from the quality assessment, a variable quality of meta-analyses and a highly variable quality of respective included studies become apparent. According to Figure 2, the conduct of study selection and data extraction by at least two independent investigators (item 2) and the usage of multiple databases, an a priori defined search strategy, and additional sources (item 3) were the strongest domains overall. Sufficient provision of study characteristics (item 6) and the consideration of scientific quality in the conclusions (item 8) were the weakest domains overall. Consequently, even if the overall scientific quality of a meta-analysis may be satisfactory, drawing conclusions while neglecting single study quality can result in misleading clinical practices. Thus, the quality in design and reporting of meta-analyses still offers potential for improvement. Further, rating of quality can be improved. For example, the rating of potential publication bias (item 10) remains unsatisfactory since the R-AMSTAR assesses whether meta-analyses consider publication bias at all, but not whether publication bias is actually present or not. Thus, from quality assessment a potential publication bias does not become apparent, which however has relevance to the confidence of interpretation of results. Lastly, the way of scoring may be revisited as the minimum score is 11 points corresponding to a high lack of quality parameters. This seems misleading considering that 25% of the total possible score indicates poor quality.

General discussion

In the following paragraphs some more general aspects are discussed. There are other agents like glucocorticoids, statins, or pioglitazone investigated in meta-analyses that are considered anti-inflammatory by some authors.[45–47] Those were not included in the present work for the following reasons: in depression a known glucocorticoid resistance and consequently lacking downregulation of inflammation exists, which questions the potential benefit and makes it difficult to assess efficacy.[138] Seemingly, statins and pioglitazone only have an indirect anti-inflammatory action.

Efficacy is not only an matter of heterogeneity but also in addressing the correct pathophysiological mechanism. If anti-inflammatory drugs are efficacious, it can be assumed that those reduce inflammatory markers. However, the application of anti-inflammatory agents does not necessarily correlate to such reduction in the course of treatment.[20,32–34] It is thus important to make well-considered decisions on which mechanism in the inflammatory pathway should be addressed and which markers should be determined to measure treatment success also on the molecular level. This will also lead to stronger prospective studies where treatment response can be predicted by certain levels of biomarkers that correspond to the chosen agents. These studies should provide a better understanding of mechanisms for tailored treatment choice and thus efficacy improvement.

Despite the more uniform and larger effect for change in depressive symptomatology of antidepressants compared to placebo, antidepressant efficacy is still an issue to discuss due to considerable and variable placebo effects.[139–141] Thus, the alternative anti-inflammatory agents were introduced to increase treatment response. However, most studies investigated these agents in add-on study designs, so the true efficacy is difficult to estimate. This is due to the usage of active antidepressant comparators which imply an inestimable placebo effect. A study design comparing the anti-inflammatory agent to a sole placebo can provide more specific information on the gain in efficacy and potentially spare patients multiple drug regimens but is mostly not done due to ethical reasons. Consequently, combining monotherapy and add-on studies in a meta-analysis is critical (many of the meta-analyses presented here did that; see also Table 1), because both designs have different implications for the interpretation of efficacy and the gain over antidepressants can only be estimated when add-on designs are included solely.

Lastly, meta-analyses should be updated regularly as new literature emerges. For example, contrary findings for celecoxib and minocycline were published just recently suggesting no gain in efficacy for celecoxib or minocycline over

the placebo condition (add-on designs) as opposed to rather strong evidence found in the presented meta-analyses.[20,34,37] A general shortcoming in this research field is the investigation of MDD patients without considering the inflammatory status. In this regard it would be interesting to take the duration of disease into account, which was rarely reported in the meta-analyses, unfortunately. Assuming that patients with a long disease history are rather treatment refractory to standard antidepressant regimen, an anti-inflammatory treatment may generate a larger effect size compared to standard treatment/placebo in those patients. This is supported by the notion that treatment resistance seems to go along with inflammatory activation.[19–21] A systematic review evaluated response to anti-inflammatory regimen in patient subgroups with and without inflammatory activation, which suggested that patients with an inflammatory signature had higher response rates to such regimen than patients without an inflammatory signature.[19] The benefit of patient stratification is also supported by recently published trials on minocycline and celecoxib.[20,34] An eminent shortcoming is that the trials summarized in the meta-analyses analyzed here included MDD patients regardless of their immune status or other known subtypes. A remaining challenge for stratification is the determination of reliable biomarkers or rather their cut-off values to distinguish inflamed and non-inflamed patient subgroups. The relevance, however, of developing precision medicine to improve treatment success using inflammatory biomarkers is an important goal for the future and has also been pointed out in recent literature.[142]

Limitations

Several limitations apply to the present work. Apart from the databases no additional sources and only meta-analyses in English language were "searched". Further, publication bias was not assessable since many meta-analyses provided funnel plots only across multiple agents (eg, Köhler-Forsberg et al) but not per single agent.[45] Thus, the information of interest to this review could not be extracted.

Furthermore, certain characteristics were not considered in the present investigation. First, age of patients could be interesting to add to the description of characteristics because a positive association with inflammation is known.[143] Second, different treatment duration in the studies and their variety when combined in meta-analyses may pose an important contributor to heterogeneity. In general, treatment duration should be an issue for discussion in this research field since the inflammatory state in depression is considered to be a chronic low-grade inflammation.[144] Third, different depression severity should be considered because it may influence the efficacy of certain drugs and may thus also have a critical impact for heterogeneity. Fourth, some meta-analyses included patients with comorbid inflammatory or immune system diseases that partly makes it difficult to discriminate treatment effects on depression. Fifth, an evaluation of different inclusion and exclusion criteria in meta-analyses may be interesting as they represent different research questions leading to inclusion of a different set of studies. Subgroup analyses should be conducted in future studies considering these variables.

In general, it is important to discuss the generalizability of study results. With respect to this review, different populations included in the meta-analyses increase the overall generalizability of findings from the various meta-analyses to a larger population. This is especially the case for omega 3 fatty acids studies, which also showed the highest variability in other characteristics. The generalizability and transfer to clinical practice is limited for highly controlled study conditions, as is the case for celecoxib meta-analyses with high consistency of characteristics across the included studies. On the other hand, applicable data for transfer to clinical guidelines, eg, information on which patient group benefits from the treatment and which dose should be administered, can hardly be concluded from results based on large variety and thus limits individualized approaches. Highly controlled study conditions are more likely to produce strong evidence (high internal validity). Consequently, weighing a limited broadness of applicability against the possibility to deduce clear conditions of application is a challenging task.

A general aspect that poses a limitation to this research field is the little understanding of the linkage between peripheral inflammatory processes and the central nervous system. Some authors discuss connecting routes in depression where immune cells and inflammatory compounds can enter the central nervous system via the blood-brain-barrier.[145,146] However, further research is warranted to elucidate how treating peripheral inflammation may affect central inflammation and reduce depressive symptoms.

Conclusion

Altogether, the presented meta-analyses demonstrate an overall significant benefit for the use of anti-inflammatory treatment regimen in major depressive disorder. However, several limitations and challenges were identified: differences between the agents are evident, where heterogeneity and diversity of characteristics, especially in omega 3 fatty acid studies, play an important role for the strength of evidence. Even though the inclusion criteria for this systematic review were defined rather homogeneous, heterogeneity can be found in several aspects like patient characteristics, treatment regimen, comparators, outcome scales and outcome values. Further, mixed scientific quality of meta-analyses with lacking definition of combination criteria, lacking consideration of quality for conclusions, and lacking rating of existence of publication bias also contributes to rather reserved conclusions about the strength of evidence. Diagnostic misclassification poses an additional challenge. Thus, methodological issues prevent the discovery of the true potential of such treatment strategies for a specific patient group and methodologically strong studies and meta-analyses are needed. However, based on the strength of evidence a ranking of agents and thus their potential for clinical applicability can be deduced: celecoxib > minocycline > omega 3 fatty acids. In future research, the named shortcomings regarding the conduct, reporting, and quality assessment of meta-analyses should be addressed. Further, biomarkers indicating inflamed patients should be investigated comprehensively to establish patient immune profiles that guide stratification for an appropriate treatment choice. Efficacy studies and meta-analyses should then be carried out again to shape clinical treatment guidelines. Further, a comprehensive analysis of safety should be carried out.

Registration and Protocol

This review was registered at PROSPERO under the registration number CRD42022296596 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=296596). A protocol was prepared in advance of conducting the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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