

It is illegal to post this copyrighted PDF on any website. Anti-Inflammatory Treatments for Major Depressive Disorder: What's on the Horizon?

Manish Kumar Jha, MD^{a,b,*}

Inflammation is associated with greater depressive symptom severity,^{1,2} resistance to commonly used antidepressants,³ differential response to escitalopram versus nortriptyline or bupropion,^{4,5} and higher likelihood of hospitalization⁶ in patients with major depressive disorder (MDD). While precise mechanisms remain unclear, a recent report found a very high correlation (coefficient = 0.855) between plasma and cerebrospinal fluid levels of C-reactive protein (CRP), suggesting that peripheral measures of inflammation are good indicators of central nervous system inflammation.⁷ Since currently available monoaminergic antidepressants are ineffective for over a third of MDD patients,⁸ targeting inflammation may be a promising avenue to develop novel mechanistically driven antidepressants.⁹ This report briefly reviews published reports and ongoing studies of anti-inflammatory treatments with potential antidepressant effects. While the role of inflammation and anti-inflammatory treatments have gained recent attention in bipolar depression,^{10,11} this report is limited in scope to studies in patients with MDD.

What's Currently Available?

Nonsteroidal anti-inflammatory drugs (NSAIDs). Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor NSAID, is the most widely studied NSAID for its antidepressant effect. In a meta-analysis of 4 randomized controlled trials (N = 160), adjunctive celecoxib was associated with 6.6 times higher rates of remission than placebo.¹² However, use of celecoxib as antidepressant augmentation was discouraged in a previous report due to the relatively small sample size for a meta-analysis, limited geographic region for 3 out of 4 studies, and lack of peer review for 1 of the reported studies.¹³ NSAIDs have poor clinical utility as antidepressant monotherapy. In a large study¹⁴ of adults with osteoarthritis (N = 1,497), ibuprofen (800 mg thrice daily) or naproxen (500 mg twice daily) and celecoxib (200 mg daily) were statistically superior to placebo in reducing depression severity. However, this difference amounted to reduction of 1 point on the 9-item Patient Health Questionnaire, suggesting lack of clinical significance.¹⁴ In another large study¹⁵ (N = 2,528) of cognitively normal elderly adults (age ≥ 70 years), there was no difference in reduction of depressive symptoms with either celecoxib (200 mg twice daily) or naproxen (220 mg twice daily) as compared to

placebo, even among those participants with significant depressive symptoms prior to treatment initiation.¹⁵

Nutraceuticals. Several nutritional supplements have shown antidepressant potential, especially in MDD patients with increased levels of inflammatory biomarkers. Shelton et al¹⁶ found that L-methylfolate was significantly more effective than placebo in MDD patients with elevated levels of CRP than those with low CRP. In another report, curcumin (500 mg twice daily) was shown to be more effective than placebo over 8 weeks of treatment in MDD patients with elevated levels of leptin.¹⁷ Omega-3 fatty acids, especially eicosapentaenoic acid (EPA), have potent anti-inflammatory properties. In a meta-analysis, supplementation with EPA-predominant formulations was superior to placebo in MDD patients, whereas docosahexaenoic acid (DHA)-predominant formulations had no significant effect.¹⁸ In a report of 155 patients with MDD who had levels of inflammatory marker available, patients with MDD who had high levels of inflammatory marker had greater reduction with EPA as compared to either placebo or DHA.¹⁹ Interestingly, placebo was superior to DHA in those with high inflammation.¹⁹ Omega-3 fatty acids as monotherapy for adolescent depression (N = 51) was not superior to placebo in a recent report,²⁰ suggesting the need for future studies with larger sample sizes. Nutraceutical supplementation may be effective in subgroups of MDD patients based on age and other comorbid conditions. For example, supplementation with EPA, curcumin, and L-methylfolate may be considered in obese adult MDD patients as both CRP and leptin levels increase with higher body mass index.

Anticytokine treatments. Arguably, monoclonal antibodies against proinflammatory cytokines are the most intriguing anti-inflammatory treatments for depression. These biologics allow precise targeting of specific immune pathways. As our understanding of the role of individual proinflammatory cytokines in pathogenesis of depression becomes clearer, these anticytokine treatments offer a path to personalized medicine. Levels of tumor necrosis factor α (TNF- α), a proinflammatory cytokine, have been reportedly elevated in MDD patients with treatment-resistant depression (TRD). Hence, Raison et al²¹ conducted a randomized placebo-controlled trial of infliximab, an anti-TNF- α monoclonal antibody, in MDD patients with TRD. While infliximab (5 mg/kg) was not superior to placebo overall, the authors noted a significant trend where higher CRP levels predicted better outcomes with infliximab. In TRD patients with CRP levels > 5 mg/L, infliximab had significantly better outcomes than placebo.²¹ To test the efficacy of anticytokine treatments in patients with chronic inflammation, Kappelmann et al²² conducted a large meta-analysis using published reports up to April 2016. They found that anticytokine treatments significantly improved depressive symptom severity in patients with chronic inflammatory conditions even after accounting for improvement in primary physical illness. Since April 2016, there have been 3 additional reports that support these findings. Interleukin 17 (IL-17) is a proinflammatory cytokine that has been implicated in pathophysiology of depression and antidepressant

^aDepartments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York

^bDepartment of Psychiatry, UT Southwestern Medical Center, Dallas, Texas

*Corresponding author: Manish Kumar Jha, MD, Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl, Box 1230, New York, NY 10029 (manish.jha@mssm.edu).

J Clin Psychiatry 2019;80(6):18ac12630

To cite: Jha MK. Anti-inflammatory treatments for major depressive disorder: what's on the horizon? J Clin Psychiatry. 2019;80(6):18ac12630.

To share: <https://doi.org/10.4088/JCP.18ac12630>

© Copyright 2019 Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

response.^{23,24} Two different monoclonal antibodies targeting IL-17 have been shown to reduce depressive symptom severity. Brodalumab, an anti-IL-17 receptor antibody, significantly reduced both depressive and anxiety symptoms as compared to placebo in a phase 3 study of patients with moderate-to-severe plaque psoriasis.²⁵ In the subset of patients in this study who had moderate to severe depressive symptoms prior to treatment initiation, rates of remission with brodalumab were 43%–47% as compared to only 9% with placebo.²⁵ These findings were remarkably similar to those with ixekizumab, an anti-IL-17-A monoclonal antibody. Using data from 3 phase 3 studies, Griffiths et al²⁶ reported remission rates of 33.6%–45.2% with ixekizumab as compared to a 17.8% remission rate with placebo. Additionally, sirukumab (N = 176) and siltuximab (N = 65), two anti-IL-6 antibodies, have also been shown to be effective in reducing depressive symptom severity among patients with rheumatoid arthritis and multicentric Castleman disease even after controlling for symptom severity of primary illnesses.²⁷ While the utility of these anticytokine treatments in patients with MDD is currently limited, clinicians may consider them for their patients with comorbid autoimmune conditions such as psoriasis and rheumatoid arthritis.

Other treatments. Several commonly used medications also affect the immune system and have been evaluated for their potential antidepressant properties. In a recent meta-analysis of 165 patients with moderate to severe depression, augmentation with statins (lovastatin, atorvastatin, simvastatin) was associated with significantly greater reduction in depression severity than placebo augmentation.²⁸ Minocycline, an anti-inflammatory tetracyclic antibiotic, has also been studied for its antidepressant potential in patients with MDD. In an open-label study of MDD patients with psychotic symptoms, augmentation of antidepressant medications (fluvoxamine, paroxetine, and sertraline) with minocycline was associated with significant reduction in both depressive and psychotic symptom severity.²⁹ Two recent double-blind randomized controlled trials^{30,31} tested the efficacy of minocycline (200 mg/d) versus placebo in patients with MDD. In the larger study³⁰ (N = 71), while there was no significant difference in depressive symptom severity as measured by the Montgomery-Asberg Depression Rating Scale, minocycline was superior to placebo on Clinical Global Impression (CGI) Improvement scores as well as on measures of quality of life and psychosocial functioning. In the smaller study³¹ (N = 41), minocycline augmentation significantly reduced depressive symptom severity as measured by the 17-item Hamilton Depression Rating Scale (HDRS-17) and CGI. Utility of minocycline in bipolar depression may also be restricted to those patients with higher pretreatment inflammatory markers such as interleukin 6.¹¹ Future studies with larger sample size and longer-term outcomes are needed to establish the clinical utility of minocycline augmentation in depression.

What's on the Horizon?

Systemic inflammation induces indoleamine 2,3-dioxygenase enzyme, which diverts tryptophan metabolism away from serotonin synthesis and toward the synthesis of neurotoxic kynurenine metabolites. In animal models, leucine, an essential amino acid, is effective in ameliorating inflammation-induced depression by preventing the uptake of kynurenine at blood-brain barrier.³² Two ongoing studies are testing the antidepressant potential of leucine in humans. While one is testing the efficacy of a 2-week course of leucine in preventing depressive symptoms induced by a single lipopolysaccharide injection in healthy human volunteers (NCT03557684), another is testing the efficacy of

leucine augmentation in a double-blind randomized crossover study of MDD patients who have inadequately responded to their ongoing antidepressant treatment (NCT03079297). Another novel antidepressant being tested is the infusion of mesenchymal stem cells (MSCs) obtained from human donors. These allogenic MSCs have been shown to exhibit immunomodulatory potential. Ongoing studies are testing its efficacy in MDD patients with treatment-resistant depression (NCT02675556) as well as with comorbid alcohol use disorder (NCT03265808). Antidepressant effects of minocycline in MDD patients with treatment-resistant depression are also being tested (NCT02456948). A recently completed pharmaceutical company-sponsored phase 2 study of sirukumab (NCT02473289) is the largest study of its kind (N = 193), testing the antidepressant effect of a monoclonal antibodies in MDD patients with elevated CRP (≥ 3 mg/L) and failure to respond to at least 1 but no more than 3 antidepressant medication trials. Among patients with CRP ≥ 3 mg/L at screening and baseline visits (N = 142), there was no significant difference either in changes in depression severity (baseline to week 12 reduction in HDRS-17) or in response and remission rates at week 12.³³ Higher baseline CRP predicted better response to sirukumab, especially in the domain of anhedonia as measured by the Snaith-Hamilton Pleasure Scale.³³

Caution in Using Anti-Inflammatory Treatments

While data in humans are lacking, preclinical studies suggest that combining NSAIDs with currently available antidepressants may result in differential outcomes based on the type of antidepressant. While use of ibuprofen blocked the antidepressant effects of selective serotonin reuptake inhibitors and tricyclic antidepressants in animal models, no similar effect was seen with either bupropion or monoamine oxidase inhibitors.³⁴ Partly consistent with these findings, MDD patients treated with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study who were on an NSAID were less likely to remit than those not on an NSAID.³⁴ The risk of opportunistic infections with use of anticytokine treatments is well recognized. Additionally, use of brodamulab was associated with 4 completed suicides in patients with psoriasis, resulting in a US Food and Drug Administration (FDA) black box warning and prescription restriction under a Risk Evaluation and Mitigation Strategy (REMS) program.³⁵ As reported by Raison et al,²¹ anticytokine treatments are inferior to placebo in TRD patients with low inflammation (CRP < 1 mg/L), suggesting that their use should be restricted to patients with ongoing systemic inflammation. Due to the risk of contaminants in nutritional supplements, clinicians should be vigilant about the source of these supplements and prescribe only pharmaceutical grade supplements when available. Finally, as none of the anti-inflammatory treatments are approved by the FDA, clinicians should restrict their off-label use to patients for whom FDA-approved treatments are either ineffective or impractical. In such cases, clinicians should use a measurement-based care approach³⁶ to monitor improvement in depressive symptom severity along with any treatment emergent adverse events with these anti-inflammatory treatments and ensure that patients are not continued on ineffective treatments for too long.

Published online: June 25, 2019.

Potential conflicts of interest: None.

Funding/support: None.

REFERENCES

1. Köhler-Forsberg O, Buttenschön HN, Tansey KE, et al. Association between C-reactive protein (CRP) with depression symptom severity and specific

It is illegal to post this copyrighted PDF on any website.

- depressive symptoms in major depression. *Brain Behav Immun.* 2017;62:344–350.
2. Jha MK, Miller AH, Minhajuddin A, et al. Association of T and non-T cell cytokines with anhedonia: role of gender differences. *Psychoneuroendocrinology.* 2018;95:1–7.
 3. Haroon E, Daguanno AW, Woolwine BJ, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology.* 2018;95:43–49.
 4. Uher R, Tansey KE, Dew T, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am J Psychiatry.* 2014;171(12):1278–1286.
 5. Jha MK, Minhajuddin A, Gadad BS, et al. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology.* 2017;78:105–113.
 6. Wium-Andersen MK, Ørsted DD, Nielsen SF, et al. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. *JAMA Psychiatry.* 2013;70(2):176–184.
 7. Felger JC, Haroon E, Patel TA, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? [published online ahead of print June 12, 2018] *Mol Psychiatry.*
 8. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905–1917.
 9. Jha MK, Trivedi MH. Personalized antidepressant selection and pathway to novel treatments: clinical utility of targeting inflammation. *Int J Mol Sci.* 2018;19(1):233.
 10. Raison CL, Pkhalov A, Siu C, et al. C-reactive protein and response to lurasidone in patients with bipolar depression. *Brain Behav Immun.* 2018;73:717–724.
 11. Savitz JB, Teague TK, Misaki M, et al. Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2x2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. *Transl Psychiatry.* 2018;8(1):27.
 12. Faridhosseini F, Sadeghi R, Farid L, et al. Celecoxib: a new augmentation strategy for depressive mood episodes: a systematic review and meta-analysis of randomized placebo-controlled trials. *Hum Psychopharmacol.* 2014;29(3):216–223.
 13. Andrade C. Antidepressant augmentation with anti-inflammatory agents. *J Clin Psychiatry.* 2014;75(9):975–977.
 14. Iyengar RL, Gandhi S, Aneja A, et al. NSAIDs are associated with lower depression scores in patients with osteoarthritis. *Am J Med.* 2013;126(11):1017.e11–1017.e18.
 15. Fields C, Drye L, Vaidya V, et al; ADAPT Research Group. Celecoxib or naproxen treatment does not benefit depressive symptoms in persons age 70 and older: findings from a randomized controlled trial. *Am J Geriatr Psychiatry.* 2012;20(6):505–513.
 16. Shelton RC, Pencina MJ, Barentine LW, et al. Association of obesity and inflammatory marker levels on treatment outcome: results from a double-blind, randomized study of adjunctive L-methylfolate calcium in patients with MDD who are inadequate responders to SSRIs. *J Clin Psychiatry.* 2015;76(12):1635–1641.
 17. Lopresti AL, Maes M, Meddens MJ, et al. Curcumin and major depression: a randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. *Eur Neuropsychopharmacol.* 2015;25(1):38–50.
 18. Hallahan B, Ryan T, Hibbeln JR, et al. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *Br J Psychiatry.* 2016;209(3):192–201.
 19. Rapaport MH, Nierenberg AA, Schettler PJ, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol Psychiatry.* 2016;21(1):71–79.
 20. Gabbay V, Freed RD, Alonso CM, et al. A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression. *J Clin Psychiatry.* 2018;79(4):17m11596.
 21. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry.* 2013;70(1):31–41.
 22. Kappelmann N, Lewis G, Dantzer R, et al. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry.* 2018;23(2):335–343.
 23. Beurel E, Lowell JA. Th17 cells in depression. *Brain Behav Immun.* 2018;69:28–34.
 24. Jha MK, Minhajuddin A, Gadad BS, et al. Interleukin 17 selectively predicts better outcomes with bupropion-SSRI combination: Novel T cell biomarker for antidepressant medication selection. *Brain Behav Immun.* 2017;66:103–110.
 25. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2016;175(2):273–286.
 26. Griffiths CEM, Fava M, Miller AH, et al. Impact of ixekizumab treatment on depressive symptoms and systemic inflammation in patients with moderate-to-severe psoriasis: an integrated analysis of three phase 3 clinical studies. *Psychother Psychosom.* 2017;86(5):260–267.
 27. Sun Y, Wang D, Salvatore G, et al. The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain Behav Immun.* 2017;66:156–164.
 28. Salagre E, Fernandes BS, Dodd S, et al. Statins for the treatment of depression: a meta-analysis of randomized, double-blind, placebo-controlled trials. *J Affect Disord.* 2016;200:235–242.
 29. Miyaoka T, Wake R, Furuya M, et al. Minocycline as adjunctive therapy for patients with unipolar psychotic depression: an open-label study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012;37(2):222–226.
 30. Dean OM, Kanchanatawan B, Ashton M, et al. Adjunctive minocycline treatment for major depressive disorder: a proof of concept trial. *Aust N Z J Psychiatry.* 2017;51(8):829–840.
 31. Husain MI, Chaudhry IB, Husain N, et al. Minocycline as an adjunct for treatment-resistant depressive symptoms: a pilot randomised placebo-controlled trial. *J Psychopharmacol.* 2017;31(9):1166–1175.
 32. Walker AK, Wing EE, Banks WA, et al. Leucine competes with kynurenine for blood-to-brain transport and prevents lipopolysaccharide-induced depression-like behavior in mice [published online ahead of print July 9, 2018]. *Mol Psychiatry.* 2018.
 33. Salvatore G, Nash A, Bleys C, et al. A double-blind, placebo-controlled, multicenter study of sirukumab as adjunctive treatment to a monoaminergic antidepressant in adults with major depressive disorder [published online Dec 6, 2018]. In: Selected Abstracts from the American College of Neuropsychopharmacology (ACNP) 57th Annual Meeting. Abstract T115. *Neuropsychopharmacology.*
 34. Warner-Schmidt JL, Vanover KE, Chen EY, et al. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by anti-inflammatory drugs in mice and humans. *Proc Natl Acad Sci U S A.* 2011;108(22):9262–9267.
 35. Brodalumab prescribing information. FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf. 2018. Accessed on July 13, 2018.
 36. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry.* 2006;163(1):28–40.

ASCP Corner offerings are not peer reviewed by the *Journal* but are peer reviewed by ASCP. The information contained herein represents the opinion of the author.

Visit the Society Web site at www.ascpp.org