**Introduction**

Mood disorders (eg, major depressive disorder [MDD] and bipolar disorder [BD]) are chronic and recurrent diseases associated with high morbidity and mortality worldwide, in which individuals are affected by a range of primary symptoms including, but not limited to, lack of motivation, anhedonia, insom-
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Selected abbreviations and acronyms

| Abbreviation | Description |
|--------------|-------------|
| BD           | bipolar disorder |
| BMI          | body mass index |
| CRP          | C-reactive protein |
| HAMD         | Hamilton Depression Rating Scale |
| IL           | interleukin |
| MDD          | major depressive disorder |
| NMDA         | N-methyl-D-aspartate |
| SMD          | standard mean difference |
| TNF          | tumor necrosis factor |

nemia, loss of appetite, and cognitive impairment. In the United States, the 12-month and lifetime prevalence of MDD are 5.3% and 13.2% respectively, with only 60% of individuals seeking or receiving psychiatric care. An international assessment of BD revealed a 1% lifetime prevalence (BDI/BDII) and 0.7% 12-month prevalence (BDI/BDII), with individuals in high-income countries seeking greater lifetime care (50.2%) than those in middle- (33.9%) and low- (25.2%) income countries. Individuals with mood disorders are also more likely to be affected by other concurrent psychiatric issues, such as substance dependence, generalized anxiety and panic disorders, as well as personality disorders, which can further exacerbate symptom presentation and severity. With a mean age of onset in early adulthood, mood disorders continue to be the leading category among mental illnesses in increased number of disability-adjusted life years (DALYs) and years lived with disability (YLDs) of those affected.

Individuals with mood disorders are also significantly more likely to be diagnosed with other chronic medical comorbidities, including cardiovascular disease, diabetes, obesity, and other metabolic syndrome-related illnesses. For example, after adjusting for age and gender, adults with BD are 1.7 to 3.2 times more likely to also be diagnosed with diabetes than those without a BD diagnosis, and individuals with MDD or BD are also 1.2 to 1.5 times more likely to be obese (body mass index [BMI] ≥30) than those without a mood disorder. In addition, the co-occurrence of mood disorders and metabolic syndrome–based risk factors or illnesses often leads to complex clinical features that are challenging to treat. This phenomenon has led some researchers to coin the term “mood-metabolic syndrome,” underscoring the relationship between these two diseases with features of bidirectionality and convergence.

Similarly, individuals affected by metabolic syndrome–related risk factors and illnesses are also at an increased risk of experiencing psychiatric symptoms. In a meta-analytic review of 15 longitudinal studies \( (n=58) \), Luppino et al found a positive association between baseline status of being overweight or obese and the development of depression later in life. In a large, community-based survey \( (n=36,984) \), McIntyre et al reported that individuals with a lifetime history of mood disorders were more likely to be obese (19%) than those without a mood disorder (15%, \( P<0.05 \)).

Although improved, current treatment options are insufficient to meet the needs of patients affected by mood disorders, as one-third of patients do not experience symptom remission after the first course of antidepressants, and a subset of patients are considered treatment-resistant. The adjunctive use of antipsychotics along with antidepressant therapy is gaining popularity; however, efficacy is difficult to assess due to the heterogeneity in tolerability and safety of antipsychotics. Current treatment options can also lead to other physical and metabolic comorbidities, such as insulin resistance, cardiovascular abnormalities, weight gain, and obesity. Antipsychotic medications specifically known to confer weight gain include clozapine, olanzapine, risperidone, and quetiapine.

The markedly increased association between mood disorders and chronic metabolic risk factors and associated illnesses suggests a common pathophysiology between these two major categories of illnesses. Specifically, multiple lines of evidence suggest a role for inflammation in the pathophysiology, phenomenology, etiology, and treatment outcomes of mood disorders. Therefore, the aim of this article is to review the literature on the role of inflammatory markers in the pathoetiology of mood disorders, with a particular focus on the opportunity that is presented by inflammation for patient stratification, treatment selection, and personalized care (see Figure 1).

A case for inflammation

The inflammatory response has evolved throughout human history to support the body to fight acute infection. However, when this system is not functioning optimally, it may lead to adverse physiological changes in the body and maladaptive behaviors, which can include depressive symptomatology (eg, sleep, cognition, motivation).
The innate immune system provides an immediate and nonspecific response to the presence of invading pathogens. Among other responses, this includes the activation of macrophages that release cytokines, such as tumor necrosis factor (TNF-α), interleukin (IL)-1, and IL-6, which are responsible for maintaining the innate inflammatory response, as well as activating the adaptive immune response.26 The adaptive immune system is responsible for pathogen-specific responses, as well as creating a memory of the new pathogen (antibody formation) in the event of future exposure. The latter system is primarily composed of lymphocytes (T cells, B-cells, and natural killer cells). B-cells secrete pathogen-specific antibodies, of which some become memory B-cells. T cells are also involved in cell-mediated response, but do not depend on the presence of antibodies.

Cytokines produced by the innate immune response (eg, IL-6, TNF-α) have been strongly linked to mood disorders and related symptoms,27 such as fatigue, cognitive impairment, and sleep disturbance.26-30 In a meta-analytic review of studies examining cytokine levels, Dowlati et al found significantly higher levels of TNF-α (weighted mean difference [WMD], 3.97 pg/mL; 95% confidence interval [CI], 2.24-5.71) and IL-6 (WMD, 1.78 pg/mL; 95% CI, 1.23-2.33) among individuals with an MDD diagnosis than in healthy controls.31 Similarly, results of a separate meta-analytic review found significantly increased levels of TNF-α, soluble TNF receptor type 1, and soluble IL-6 receptors among individuals with BD (n=761) compared with controls (n=919).22 Increased peripheral levels of soluble IL-2 receptors and IL-4—indicators of T-cell activation and, subsequently, markers of adaptive immunity—have also emerged as possible biomarkers of depression.29,33

C-reactive protein (CRP) is a substance produced by the liver and is also indicative of increased inflammation. Although it has been commonly used as a marker for increased inflammation associated with heart disease and stroke, it is now also a predictor of mood disorders.34,35 Furthermore, individuals with metabolic abnormalities are also more likely to present with increased levels of inflammation. For example, since adipose tissues produce IL-1 and IL-6,36 which are precursors of CRP, individuals who are overweight and obese are more likely to have higher levels of this protein and thus are more likely to be prone to symptoms of mood disorders. Since levels of this protein are easily detected through nonfasting blood analysis,35,37 it is a commonly used indicator of inflammation in both research and clinical settings.

Interestingly, when individuals with autoimmune diseases are given inflammation-based therapies (eg, interferon, typhoid vaccination, or endotoxin), these individuals are at an increased risk of presenting with mood disorders.38,39 Consequently, there is evidence to support bidirectionality between mood disorders and inflammation, which is further complicated and fueled by the presence of metabolic abnormalities.

There are a number of possible mechanisms that may be involved in the inflammation-induced mood presentation, which has been explored at length elsewhere.40-42 However, the pathophysiology of inflammation in mood disorders includes, but is not limited to, changes in the bioavailability and metabolism of neurotransmitters, increased activation of the hypothalamic-pituitary-adrenal (HPA) axis, increased levels of oxidative stress, increased activation of microglia, and decreased neural plasticity.43,44 In particular, presence of inflammation in the brain has been shown to affect glutamate release and uptake, oxidative stress, and excitotoxicity.41 Therefore, targeting inflammatory markers as an avenue to treat mood disorders may present a personalized approach to care. Treatment options for individuals who present with increased markers of inflammation include anti-inflammatory agents (eg, infliximab), antiglutamate agents (eg, ketamine), and L-methylfolate. These three major avenues for treatment selection will be explored further.
Anti-inflammatory agents for mood disorders

In light of the compelling evidence linking inflammation to mood disorders, a number of studies have been undertaken to examine the role of anti-inflammatory agents as a therapeutic option for mood disorders. Kohler et al conducted a meta-analysis of randomized, placebo-controlled clinical trials evaluating the antidepressant effect of anti-inflammatory agents. Ten trials (n=4258) evaluated the effect of nonsteroidal anti-inflammatory agents (NSAIDs), and four trials (n=2004) evaluated cytokine inhibitors. The pooled effect size revealed a medium antidepressant effect (standard mean difference [SMD], -0.34; 95% CI, -0.57 to -0.11), particularly among patients with an MDD diagnosis (SMD, -0.54; 95% CI, -1.08 to -0.01) as opposed to individuals displaying depressive symptoms without a formal diagnosis (SMD, -0.27; 95% CI, -0.53 to -0.01).

Similarly, Rosenblat et al conducted a meta-analytic review of randomized clinical trials examining the antidepressant effect of adjunctive anti-inflammatory agents among patients with BD. Of the 10 completed RCTs reviewed, 5 (n=140) evaluated treatment with omega-3 fatty acids, two evaluated N-acetylcysteine (n=76), and one evaluated celecoxib (an NSAID, n=23), aspirin (n=30), and pioglitazone (n=44) each. The overall SMD (n=312) revealed a medium effect size of -0.40 (95% CI, -0.14 to -0.65, P<0.01) for the use of an adjunctive anti-inflammatory agent in depression treatment when compared with conventional therapy alone.

Raison et al conducted a double-blind, randomized, placebo-controlled trial examining the effect of infliximab, a TNF-α antagonist, among individuals with MDD (n=60). Although there was no significant change in scores on the 17-item Hamilton Depression Rating Scale (HAMD-17) between the two treatment groups across time, a reduction in HAMD-17 scores was observed when analyses were stratified by baseline inflammatory levels, such that subjects with high levels of inflammation at baseline (ie, high-sensitivity CRP [hs-CRP] >5 mg/L) who received infliximab exhibited a greater reduction in HAMD-17 scores than subjects with low levels of baseline inflammation. This study provides support for the stratification of individuals with MDD to inform treatment selection, in that patients with increased baseline levels of inflammation may be more responsive to anti-inflammatory treatment than a nonstratified heterogeneous group of MDD patients.

In light of evidence supporting a stratified approach to participant selection, baseline inflammatory markers are part of an ongoing clinical trial to examine the potential therapeutic effect of infliximab among patients with bipolar depression (ClinicalTrials.gov ID = NCT02363738). The inclusion criteria for baseline inflammation include presence of any one of the following: (i) central obesity (measured by increased ethnicity-specific waist circumference or a BMI greater than 30 kg/m²) and a) raised triglycerides, b) reduced high-density lipoprotein cholesterol, or c) raised blood pressure; (ii) diabetes; (iii) inflammatory bowel disorder (ie, ulcerative colitis, Crohn disease); (iv) rheumatological disorders (eg, rheumatoid arthritis); (v) psoriasis; (vi) daily cigarette smoking (minimum of half a pack); or (vii) CRP greater than 5 mg/L. These criteria were generated based on results of previous research implicating these factors in increased levels of inflammation.

Antiglutamate medications for mood disorders

Glutamate is the major excitatory neurotransmitter of the nervous system, and individuals with mood disorders present with abnormal glutamate metabolism that may be augmented by increased levels of inflammation. In contrast with the view of monoamines as the primary target for depression treatment in previous decades, there has been a paradigm shift in recent years to place abnormal glutamate neurotransmission at the center of symptoms presented by individuals with mood disorders.

Glutamate synapses are plastic and can undergo structural and functional changes that can be both adaptive and maladaptive. Neuroplasticity at glutamate-based synapses enhances learning and memory. However, dysfunction of the glutamatergic system in the limbic and cortical areas can lead to maladaptive changes, such as dendritic remodeling, synaptic reductions, and volume changes, similar to the changes observed in individuals with mood disorders. Inflammation may be a contributor to abnormal glutamate regulation among individuals with mood disorders by inducing astrocytic dysfunction, which subsequently has a negative impact on glutamatergic regulation.
Using magnetic resonance spectroscopy, Haroon et al examined whether increased inflammation correlated with increased glutamate in the left basal ganglia and dorsal anterior cingulate cortex, and if these abnormal changes in glutamate levels impacted behavioral outcomes in 50 patients who had an MDD diagnosis and no previous treatment. Inflammation was measured on the basis of plasma and cerebrospinal fluid inflammatory markers, with a focus on plasma CRP. They found that elevated levels of log-transformed plasma CRP significantly correlated with increased levels of log left basal ganglia glutamate in the left basal ganglia, and the latter increase was, subsequently, also found to be associated with anhedonia and psychomotor retardation.38

Therefore, elevated levels of inflammation present clinicians with an avenue for using not only anti-inflammatory agents but also glutamate agents. Glutamate can be regulated at a number of different sites, including N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, glutamate transporters, and metabotropic receptors. Of the available drugs, ketamine, an NMDA receptor antagonist, has shown great promise against the effects of elevated glutamate.39 In a meta-analytic review of nine randomized controlled trials, participants (192 MDD, 34 BD) receiving ketamine reported significantly reduced symptoms of depression compared with those receiving placebo (SMD, -0.99; 95% CI, -1.23 to -0.75; Prhoe<0.01).40 In the most recent examination of ketamine in a double-blind, randomized, placebo-controlled clinical trial, a significant reduction was observed in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline among participants receiving ketamine compared with those receiving placebo.41 Although memantine, another NMDA receptor antagonist, has failed to show efficacy as an antidepressant treatment on its own,52 there is some initial evidence to suggest that it can be effective in maintaining the effects of initial administrations of ketamine and lamotrigine.93,64

Lamotrigine also acts directly on the glutamate system and has shown similar antidepressant effects to other psychiatric medications, including lithium, olanzapine plus fluoxetine, citalopram, and inositol.65 Traxoprodil is another NMDA receptor antagonist that has shown therapeutic effects as an adjunctive treatment with paroxetine.66 Although there is some preliminary evidence of antidepressant effects, there is insufficient evidence to conclude the efficacy of other NMDA-receptor–based therapeutics, such as lanicemine,52,67 nitrous oxide,68 and amantadine at this time.69 Drugs binding at the glycine site of NMDA receptors, such as d-cycloserine70 and rapastinel,71 also show promise of antidepressant efficacy.

Benzothiazole drugs possess antimicrobial, analgesic, anti-inflammatory, and antidiabetic properties. Riluzole is one such example of a benzothiazole drug that has been shown to be fast acting in the alleviation of depressive episodes in MDD72,73 and BD74 in open-label trials aimed at restoring glutamatergic function to normal levels. Inflammation-based glial pathology may be associated with glutamate excitotoxicity,75,76 and riluzole is hypothesized to aid in glia-mediated glutamate clearance.77,78 Therefore, the glutamate system involves several pathways providing a number of different targets for new drug therapy, some of which have been investigated and provide initial evidence of efficacy.

**L-methylfolate for mood disorders**

Folic acid and its biologically active form, L-methylfolate, are important for the normal production of neurochemicals, such as serotonin, melatonin, dopamine, epinephrine, and norepinephrine.79 Folic acid is converted to its active form by the enzyme methylenetetrahydrofolate reductase (MTHFR), after which L-methylfolate crosses the blood-brain barrier into the central nervous system. However, many individuals with psychiatric disorders, including those with mood disorders, have polymorphisms at the gene site for this enzyme, contributing to reduced bioavailability of L-methylfolate in the central nervous system.80,82 Tetrahydrobiopterin (BH4) is a critical enzyme cofactor that is involved in the production of neurotransmitters, such as serotonin, dopamine, and norepinephrine. The presence of inflammation or oxidative stress can lead to the irreversible degradation of BH4. Folic acid and L-methylfolate play an important role in increasing the bioavailability of BH4.83 Therefore, evaluating patients for MTHFR gene polymorphisms may present with another avenue for targeted treatment and personalized care.

Papakostas et al conducted a randomized controlled trial examining the antidepressant effect of adjunctive L-methylfolate (15 mg/day for 60 days) in individuals with MDD with an inadequate response to selective serotonin reuptake inhibitor treatment (n=75). Par-
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Participants who received l-methylfolate reported improvements on the 28-item HAMD (HAMD-28) that was of medium effect size ($d=0.41$, $P<0.05$). Among individuals with baseline inflammatory/metabolic abnormalities (BMI $\geq 30$ kg/m$^2$, elevated levels of CRP or 4-hydroxy-2-nonenal, low $S$-adenosylmethionine/$S$-adenosylhomocysteine ratio) or genetic variations in l-methylfolate metabolism, there was an even greater improvement in scores on the HAMD-28. In a post hoc evaluation of this data with the HAMD-17, Shelton et al found greater treatment effects of l-methylfolate among individuals with a BMI greater than or equal to 30 kg/m$^2$, specific inflammatory markers (TNF-α, IL-8, hs-CRP, and leptin) or a combination of BMI at or above 30 and certain inflammatory markers (TNF-α, IL-8, IL-8, hs-CRP, and leptin). Again, with the use of adjunctive l-methylfolate treatment, greater treatment efficacy appears when patients are stratified not only on the basis of insufficient levels of l-methylfolate in the central nervous system, but also on the basis of direct or indirect markers of inflammation.

Discussion/conclusion

This review aimed to describe the extant literature on the presence of increased inflammation in individuals with mood disorders, as well as suggest novel therapeutic opportunities afforded by this relationship. Current monoamine antidepressant therapies are ineffective in many individuals with mood disorders, underscoring our incomplete understanding of the etiology of mood disorders and encouraging a reconceptualization of how best to treat them. Moreover, current psychiatric medications present with delayed onset of therapeutic benefits and unfavorable safety profiles and side effects. Moving forward and considering the foregoing limitations, novel treatments for mood disorders need to be increasingly comprehensive, multifactorial, effective, and well tolerated.

The limitations of current models of mood disorders and lack of effective treatment development have led to the consideration of several other physiological processes, biomarkers, and neurochemicals as central to the development and treatment of depression. Inflammation presents yet another inroad where health care providers can adopt a personalized approach to psychiatric care for their patients. As this review indicates, extant evidence supports the use of anti-inflammatory–, ant glutamate– and l-methylfolate–based treatments to enhance the efficacy of traditional psychiatric medications. In particular, a number of inflammation-based targets are currently being investigated to this effect and may soon provide physicians with alternative and increasingly patient-specific treatment options.

Individuals with mood disorders are also affected by significant declines in their cognitive function. Although traditional psychiatric treatments may help with improvements in mood, cognitive impairment remains a complaint of patients in symptomatic remission and continues to impair functional capacity. Metabolic syndrome–related illnesses and risk factors, such as abdominal obesity, diabetes, and cardiovascular disease, are also associated with cognitive impairment among those with mood disorders. Furthermore, increased levels of inflammatory markers were found to be associated with cognitive dysfunction among people with BD. Similarly to other domains affected in mood disorders, immune dysregulation also appears to be mediating the bidirectional effect of metabolic comorbidities and cognitive dysfunction.

Lastly, the prioritization of addressing primary psychiatric symptoms, both by patients and health care providers, has often been at the expense of other physical health parameters, which, in turn, can have a negative impact on psychiatric outcomes. In addition to the provision of pharmacological and/or psychotherapeutic treatment of psychiatric illnesses, health care providers are encouraged to work with their patients to ensure that they are maintaining a well-balanced diet and engaging in regular physical activity. A balanced and nutritious diet, such as the Mediterranean diet, has been shown to have anti-inflammatory properties, as it is high in fruits, vegetables, legumes, monounsaturated and polyunsaturated fatty acids compared with the high carbohydrate–based diets prevalent in North America.

In addition to addressing metabolic comorbidities in mood disorders, regular physical activity can also help reduce levels of inflammation. In a sample of 13 748 adults who completed the National Health and Nutrition Examination Survey (1988-1994), CRP levels were lower among individuals who engaged in exercise during the previous month than individuals who did not engage in exercise. Furthermore, there was a dose-response relationship between intensity of physical activity and CRP levels, with greater CRP reductions seen among patients who engaged in higher-intensity exer-
exercise. Individuals with mood disorders are more likely to lead sedentary lifestyles, which can lead to increases in markers of chronic inflammation. For example, in a cross-sectional examination of 250 patients with psychosis, levels of CRP were significantly greater among patients who reported sedentary lifestyles. Therefore, patients should be encouraged to reduce the amount of time they spend in stationary positions and take active breaks in between their sedentary/stationary activities. In addition, it should be communicated to patients that a sedentary lifestyle, independent of physical activity engagement, is associated with risk factors for metabolic illness and chronic inflammation. Overall, addressing inflammation both through pharmacological and nonpharmacological means provides novel avenues for treatment selection, as well as an opportunity to revisit known and effective ways of managing physical health and, subsequently, inflammation.

**Conclusions**

There is a greater understanding of and appreciation for the role of physical health in the brain and mood disorders. In particular, addressing inflammation, both through pharmacological and nonpharmacological means, may provide novel avenues for treatment selection in the future. In addition to the direct and indirect effects on mood, inflammation may also directly impact cognition and thus provides a unique avenue for treatment selection in this particular domain as well. Therefore, this field of research has the potential to affect patients with mood disorders on a number of different levels and will continue to be explored in the coming years. The role of poor physical health in mood disorders also presents an opportunity to revisit known and effective ways of managing physical health in patients, such as the appropriate and timely management of physical comorbidities and the adoption of healthy lifestyle choices.

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La inflamación: oportunidades para la estratificación del tratamiento de los pacientes con trastornos del humor

Los trastornos del humor continúan siendo una carga significativa para los pacientes que los sufren, lo que se traduce en una significativa incapacidad asociada con la enfermedad y una mortalidad prematura. Además de la alteración del ánimo, los individuos también presentan otras comorbilidades como anhedonia y deterioro cognitivo. Aunque en las últimas décadas han habido significativos avances en la terapia psiquiátrica, la eficacia terapéutica (como la remisión sintomática, la falta de recuperación funcional y la modificación de la enfermedad) continúa siendo una limitación importante. En consecuencia, existe una necesidad urgente de identificar nuevas aproximaciones capaces de orientar las necesidades antes mencionadas, proveyendo las bases para la exploración de modelos conceptuales y oportunidades terapéuticas que consideren la inflamación como un factor clave en el desarrollo del trastorno anímico. En parte, a causa de comorbilidades metabólicas una gran proporción de sujetos con trastornos del ánimo también tienen un desbalance en el medio inflamatorio. El objetivo de esta revisión es clarificar la evidencia que involucra a la inflamación en varios sistemas efectores en los trastornos del ánimo, enfocándose particularmente en la intercomunicación con las señales glutamatérgicas y las señales del sistema inmune, como también los parámetros metabólicos (como la biodisponibilidad de L-metilfolato). Este artículo también revisa brevemente los agentes nuevos y reutilizados, capaces de apuntar al sistema inflamatorio inmune innato y posiblemente corregir el medio inmunoinflamatorio (como infliximab).

L’inflammation, une perspective pour la stratification du traitement des patients ayant des troubles de l’humeur

Les troubles de l’humeur pèsent toujours lourdement sur ceux qui en sont atteints, entraînant une incapacité significative associée à la maladie et une mortalité prématurée. En plus des troubles de l’humeur, les sujets présentent aussi d'autres comorbidités comme l’anhedonie et les troubles cognitifs. Ces dernières décennies, le traitement psychiatrique a bénéficié d’avancées notables mais son efficacité (rémission des symptômes, manque de guérison fonctionnelle et modification de la maladie) est toujours une limite importante. Afin de satisfaire les besoins décrits ci-dessus, il est donc urgent d’identifier de nouvelles approches à partir desquelles il sera possible d’explorer des modèles conceptuels et des traitements considérant l’inflammation comme un facteur clé du développement des troubles de l’humeur. Un grand nombre de personnes ayant des troubles de l’humeur présentent également un déséquilibre du milieu inflammatoire, en partie à cause de la présence de comorbidités métaboliques. Cet article a pour but de souligner les données en faveur de l’implication de l’inflammation dans différents systèmes effecteurs des troubles de l’humeur, en s’intéressant particulièrement à l’intercommunication avec la signalisation glutamatérgique, la signalisation du système immunitaire, ainsi qu’aux paramètres métaboliques (par exemple la biodisponibilité du L-méthylfolate). Cet article analyse rapidement les agents nouveaux et ceux existants mais « reconvertis » qui sont capables de cibler le système inflammatoire immunitaire naturel et de corriger éventuellement un milieu immunitaire/inflammatoire anormal (par exemple l’infliximab).