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Current evidence on immune-driven depression

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Purpose of review
This review summarizes recent evidence on immune-driven depression, a subtype of major depressive disorder (MDD) characterized by low-grade inflammation, energy-related symptoms and metabolic disturbances. This subtype is associated with worse outcomes and distinct antidepressant responses. Considering inflammatory features may help clinicians tailor MDD management, particularly by informing lifestyle measures and targeted interventions. The review highlights studies describing features of immune-driven depression, discussing mechanistic pathways, and evaluating mechanism-based interventions.

Recent findings
Novel mechanistic evidence includes sex-specific associations between inflammatory markers and depressive symptoms, effects of inflammation on motivation and immuno-metabolic interactions. These findings have informed stratified and enriched trial designs preselecting patients with inflammatory profiles. International initiatives integrate clinical, biomarker, neuroimaging and genetic data to define reproducible signatures. Novel interventions include GLP-1 receptor agonists, more focus on dopaminergic agents and low-dose interleukin-2.

Summary
Current evidence supports immune-driven depression as a clinically relevant MDD subtype. Indicators such as hsCRP, comorbid metabolic or inflammatory conditions and motivational anhedonia may help clinicians recognize at-risk patients. Most intervention trials remain limited by small, heterogeneous samples and nonspecific outcome measures. Advances in biomarker-guided stratification represent important steps toward precision psychiatry, aiming to develop tailored, mechanism-based treatments for MDD.

Keywords
anti-inflammatory treatment, immune-driven depression, immunopsychiatry, inflammation, precision psychiatry

INTRODUCTION: INFLAMMATION AND PSYCHIATRIC ILLNESS

As medicine is moving away from a one-size-fits-all treatment model towards a more individualized approach, there is growing interest in defining biologically meaningful subgroups within heterogeneous patient populations to guide tailored treatments. Some medical specialties, such as oncology, now routinely use mechanism-based treatments improving prognosis. In contrast, psychiatry is not yet ready to integrate this kind of precision. Within this context, however, immunopsychiatry has become a promising and rapidly expanding field [1▪▪].

Inflammation is associated with and causally related to psychiatric disorders

We have gained a strong insight into the link between chronic immune system activation and psychiatric disorders, including depression, schizophrenia, bipolar disorder and posttraumatic stress disorder [2,3▪]. Large-scale epidemiological studies have consistently reported associations between inflammation and psychiatric disorders. In depression specifically, multiple cross-sectional studies have replicated associations between depressive symptoms and higher peripheral levels of pro-inflammatory cytokines, such as certain interleukins [e.g. interleukin (IL)-6, IL-1β], tumor necrosis factor (TNF) and C-reactive protein (CRP) [2,4]. Longitudinal research further supports the idea that inflammation not only accompanies but also precedes psychiatric disorders. This is supported by immune challenge studies, where administration of pro-inflammatory agents such as

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KEY POINTS

- Several clinical and biological indicators may help clinicians identify patients at risk for immune-driven depressions.
- Novel mechanistic evidence includes sex-specific biomarker associations and disrupted dopaminergic reward pathways linking inflammation to motivational anhedonia.
- New interventions being tested include GLP-1 receptor agonists and low-dose IL-2.
- Stratified and enriched trial designs now preselect patients with elevated inflammatory biomarkers and/or immuno-metabolic profiles.

TNF-α in mice [5], lipopolysaccharide (LPS) in rodents and humans [6] and interferon alpha (IFN-α) in patients with melanoma [7] consistently induces depressive-like symptoms. A recent prospective study using data from 585 279 participants found that elevated baseline levels of inflammatory markers, including CRP, were prospectively associated with an increased risk of developing affective and psychotic symptoms over a 30-year follow-up period [8▪]. These results were validated in a UK biobank cohort of 485 620 individuals.

Importantly, none of the major psychiatric disorders can be considered primary inflammatory disorders, but low-grade persistent inflammation does play an important role in subgroups of the affected individuals. Immune dysregulation represents a shared biological mechanism driving, often more severe, symptom trajectories, independent of the specific diagnosis [1▪▪]. This is supported by recent transdiagnostic research showing that disease severity across psychiatric diagnoses is consistently associated with elevated levels of pro-inflammatory cytokines [9▪].

Inflammation is contributing to depressive symptoms

Depression is the most extensively studied in relation to immune dysregulation. One of the most reproducible constructs is the existence of an immune-driven subtype of depression: a situation where the development and/or continuation of depressive symptoms is mechanistically driven by chronic immune dysregulation.

The increasing interest in personalized psychiatry causes a growth of mechanistic and clinical evidence on immune-driven depressions. Understanding how peripheral immune activation translates into mood changes can help clinicians identify at-risk patients, interpret biomarkers and consider mechanism-based interventions. This review provides an overview of the latest evidence with a focus on the prevalence and clinical presentation of immune-driven depression, mechanistic pathways linking low-grade inflammation with depression, and clinical management.

PREVALENCE AND PRESENTATION OF IMMUNE-DRIVEN DEPRESSIONS

Approximately 30% of patients with major depressive disorder (MDD) present with clinical and biological features suggestive of an immune-driven subtype. This subtype is characterized by low-grade systemic inflammation, commonly reflected in blood markers such as elevated high-sensitivity CRP (e.g. a blood hsCRP of $\geq$3 mg/l), IL-6 or glycoprotein acetyls; atypical, energy-related symptoms such as motivational anhedonia (i.e. difficulty feeling motivated for activities that require some level of effort), hypersomnia, hyperphagia, weight gain, leaden paralysis and profound fatigue; which are often but not always accompanied by concurrent metabolic abnormalities such as higher BMI, insulin resistance and dyslipidemia [10▪▪,11].

Identification of immune-driven major depressive disorder subtype

To accurately identify this immune-driven subtype in clinical practice, growing consensus suggests that a combination of clinical and biological indicators across multiple domains is most helpful. For example, Zwiep *et al.*, using data from 1077 individuals with MDD from the longitudinal Netherlands Study of Depression and Anxiety (NESDA) cohort, showed that individuals with higher CRP levels (>1 mg/l) and elevated atypical, energy-related symptom scores exhibited higher circulating levels of all inflammatory and metabolic markers, including glycoprotein acetyls, BMI, waist circumference and leptin [12▪].

In parallel, Donnelly *et al.* performed an immunometabolic biomarker study in young adults (N=309 with MDD). They identified a somatic-inflamed group, characterized by higher IL-6 and neutrophils with worse fatigue, lower motivation and greater depression severity over 5 years compared to the peers with lower inflammatory markers [13▪]. Similarly, Foley *et al.* found that higher IL-6 activity was associated with more somatic symptoms, higher depression severity, reduced psychomotor speed and a lower quality of life. Importantly, IL-6 levels were found to strongly correlate with traditional inflammatory markers such as CRP and TNF-α [14▪]. This positive

relationship between IL-6 and CRP appears to be sex-specific. Lombardo *et al.* already reported in 2022 that this correlation was present in females but not in males [15], a finding that was recently replicated within the NESDA-cohort by Van den Noortgate *et al.* (Van den Noortgate *et al.*, unpublished data).

Immune-driven depression also includes postinfectious presentations (e.g. following COVID-19) and cases comorbid with autoimmune conditions. Although the sources of inflammation may differ in these cases, they appear to share common inflammatory pathways, often present with more chronic and severe symptom trajectories, and have shown reduced response to standard antidepressants [1▪▪,10▪▪]. Table 1 summarizes key indicators across multiple domains that can help identify immune-driven depression. Based on the recent (frame)work of Penninx *et al.*[10▪▪], this approach can be used in both research and clinical settings to better capture this prognostically relevant subgroup.

HOW INFLAMMATION LEADS TO DEPRESSION

The evidence summarized in Table 2 highlights the established knowledge and recent evidence on how genetic predisposition and early life stress form a vulnerability for chronic immune dysregulation later in life, while acute infections, autoimmune disease and adverse lifestyle/metabolic factors act as triggers of sustained inflammation. These interact with biological systems, including the hypothalamic-pituitary-adrenal axis (HPA)-axis, mitochondrial function and metabolic pathways, creating a loop of inflammation and stress.

From peripheral to central inflammation

As outlined in Fig. 1, multiple triggers can cause peripheral inflammation, reflected in elevated pro-inflammatory cytokines and altered circulating myeloid and lymphoid cells. These cytokines and cells can cross or signal across the blood–brain barrier (BBB), activate microglia and astrocytes, and set off neuroinflammation [38▪]. Neuroinflammation disrupts neurotransmitter systems, reduces neurotrophic support (BDNF) and alters structure and function in mood-relevant brain areas (hippocampus, amygdala, prefrontal cortex, striatum). Recently, Shang *et al.* have indirectly visualized, with advanced MRI techniques, that the BBB permeability was significantly higher in MDD ($N=23$ vs. $N=18$ healthy controls) and positively correlated with the depression severity [39▪]. This higher permeability was confirmed via blood-based biomarker panels [40▪]. BBB integrity is

Table 1. Biological and clinical indicators of immune-driven depression

Domain	Indicators of immune-driven depression	Clinical implications
Clinical symptoms [10▪▪,16▪]	- Hypersomnia - Hyperphagia - Fatigue - Leaden paralysis - Motivational anhedonia = atypical, energy-related symptoms	- Symptom clusters may suggest immune system involvement - Ideally assessed using symptom scales capturing these domains (e.g. IDS-30 or IDS-SR)
Inflammatory markers [8▪,12▪,14▪,17▪]	- Higher levels of hsCRP, IL-6, TNF-α, glycoprotein acetyls, WBC and neutrophils - Composite indices of inflammation (e.g. NLR, IL-6 activity/bioavailability ratio, panels analyzing multiple biomarkers) = systemic low-grade inflammation	- hsCRP $\geq$3 or hsCRP>1 combined with symptom profile may indicate immune activation - Composite indices may increase specificity by integrating multiple markers rather than relying on a single cytokine
Metabolic disturbances [10▪▪,13▪,18▪]	- Elevated waist circumference and/or BMI - Insulin resistance - Dyslipidemia - Leptin resistance	- Metabolic disturbances suggest an immuno-metabolic phenotype - May guide interventions targeting metabolic inflammation (e.g. diet, exercise, GLP-1 agonists)
Trajectory [9▪,19▪–21▪,22,23▪]	- Postinfectious onset - Comorbid auto-immune disease - Immuno-metabolic (e.g. metabolic syndrome) - Severe and chronic symptoms - Poor antidepressant response	- History and course can indicate underlying immune involvement - May warrant early consideration of add-on anti-inflammatory

BMI, body mass index; GLP-1, glucagon-like peptide-1; hsCRP, high-sensitivity C-reactive protein; IDS-30, 30-item version of inventory of depressive symptomatology; IDS-SR, self-report version of inventory of depressive symptomatology; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; TNF-α, tumor necrosis factor-alpha; WBC, white blood cells.

Table 2. Established knowledge and recent evidence of vulnerability factors, immune triggers, and biological dysregulation underlying immune-driven depression

	Underlying vulnerability	
	Established knowledge	**Recent evidence**
Genetics	- Genetic variants in MDD predispose to immune dysregulation and vice versa [24].	- Shared genetic correlations between immune diseases and psychiatric symptoms, suggesting shared transdiagnostic pathways of vulnerability [25▪].
Early life stress	- Childhood maltreatment and ACEs lead to a primed immune system, often associated with higher CRP and IL-6 in adulthood.	- CM is linked with transdiagnostic increases in pro-inflammatory markers, with IL-6 acting as a key mediator between CM and adult psychiatric diagnoses [26▪▪]. - CRP and IL-6 mediate the relationship between ACEs and depressive symptoms [27▪]. - Parental depression and unsupportive parenting predict pro-inflammatory phenotype [28▪].
	Immune system triggers	
	Established knowledge	**Recent evidence**
Infections	- Acute infections lead to sickness behavior (fatigue, anhedonia, withdrawal); usually adaptive and transient. - Persistent immune activation transforms protective state into sustained mood disturbances and motivational deficits [29▪].	- Influenza virus components in the hippocampus in mice induces anxiety- and depressive-like behaviors [23▪]. - MDD prevalence in the US rose to 12.4% during the COVID-19 pandemic, mostly among young adults (16.6%) and females (14.7%) [29▪]. - COVID-19 is linked to structural/functional brain changes and widespread neuroinflammation [21▪,30▪]. - Postacute infection syndromes (PAIS) often share symptoms with MDD and likely common underlying mechanisms [31]. - Illnesses like depression may in a substantial amount of cases, reflect postviral syndromes [32▪].
Autoimmune diseases	- AI patients associated with higher risk of affective disorders.	- AI diseases nearly double MDD risk [22]. - IBD patients report anxiety/depression in up to 35%, especially in active phases. Proteomics in depressed IBD patients identified elevated FGF-23 and CXCL1, suggesting specific immunological pathways [17▪].
Lifestyle and metabolic factors	- Obesity, insulin resistance and sedentary lifestyle lead to low-grade systemic inflammation.	- Framework explains how an adverse metabolic profile, chronic stress and inactivity lead to a vulnerability for immune-driven MDD and may interact synergistically with infection- or AI-related triggers [10▪▪]. - Stress-gut-brain axis emerging as vulnerability pathway [33▪].
	Biological dysregulation	
	Established knowledge	**Recent evidence**
HPA axis	- Acute stress: activation HPA axis leads to cortisol release, which suppresses inflammation via GC receptors. - Chronic stress: GC resistance leads to persistent pro-inflammatory state with high cortisol and high cytokines.	- Stress-gut-HPA interactions show that microbiota disruption amplifies systemic inflammation [33▪]. - Interventions, such as selective GR-antagonists, have shown inconclusive results in unselected patient populations, suggesting correction of GC resistance may only work in a subgroup of patients [34▪]. - HPA axis and immune measures associate poorly in MDD under baseline conditions. Challenge paradigms show blunted lymphocyte reduction, pointing to altered HPA-immune crosstalk [35▪▪].

Table 2 (*Continued*)

	Biological dysregulation	
	Established knowledge	**Recent evidence**
Mitochondrial dysfunction	- Immune activation (e.g. viral infection) can impair mitochondrial energy metabolism, linking postviral chronic inflammation to mental health symptoms [36▪].	- SARS-CoV-2 infection inhibits mitochondrial oxidative phosphorylation, resulting in more ROS production and the release of mitochondrial DNA, which amplifies inflammatory signaling [20▪] - Inflammation-induced mitochondrial impairment is common in MDD and associated with fatigue and cognitive deficits, even in the absence of acute infection. Higher CRP or IL-6 is associated with more mitochondrial abnormalities [37].
Metabolic disturbances	- Immune-drive depression often presents with metabolic disturbances [10▪▪,38▪].	- Chronic inflammation itself can promote insulin resistance and alter lipid metabolism, creating a vicious cycle that sustains metabolic dysfunction and mood disturbances. GLP-1 receptor agonists, developed for type 2 diabetes and weight loss, reduce peripheral inflammation and show promise for improving mood and neurodegenerative outcomes [10▪▪].

ACEs, adverse childhood experiences; AI, auto-immune; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CM, childhood maltreatment; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; CXCL1, C-X-C motif chemokine ligand 1; ECT, electroconvulsive therapy; FGF-23, fibroblast growth factor 23; GC, glucocorticoid; GLP-1, glucagon-like peptide-1; GR, glucocorticoid receptor; HPA axis, hypothalamic–pituitary–adrenal axis; IBD, inflammatory bowel disease; IFN-α, interferon-alpha; IL-6, interleukin-6; LPS, lipopolysaccharide; MDD, major depressive disorder; PAIS, post-acute infection syndromes; QoL, quality of life; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TNF-α, tumor necrosis factor-alpha; US, United States.

now being explored as a therapeutic target in immune-driven depression [41▪].

Central inflammation disturbs monoamine synthesis

Neuroinflammatory responses can directly impair monoaminergic neurotransmission, reducing the availability of serotonin, dopamine and norepinephrine by multiple mechanisms [38▪].

The kynurenine pathway and serotonin

One pathway involves cytokine-induced activation of indoleamine 2,3-dioxygenase (IDO) diverting tryptophan away from serotonin synthesis toward kynurenine (KYN) production. This was hypothesized to reduce serotonin and produce neuroactive KYN metabolites affecting gluteamergic signaling and oxidative stress [42▪]. However, evidence suggests a more complex picture, with inconsistent findings that are often dependent on clinical states [43]. For example, Skorobogatov *et al.* found that the clinically relevant kynurenine pathway (KP) markers (e.g. quinolinic acid vs. kynurenic acid) may differ across patient subgroups and disease states [44,45▪], with more acutely symptomatic patients demonstrating stronger KP downregulation. Importantly, Nikkheslat *et al.* demonstrated a sex-specific relationship in a longitudinal cohort of adolescents, in which female adolescents at risk for/with MDD showed reduced levels of neuroprotective KYN metabolites [46▪]. Additionally, preclinical evidence has now shown that ketamine has the potential to inhibit the KP, leading to pro-neurogenic and anti-inflammatory effects [47].

Reward pathways and dopamine

One of the most consistent findings is the inhibitory effect of inflammation on reward-related dopaminergic pathways, as already reviewed in 2021 [48]. Inflammatory cytokines can decrease tetrahydrobiopterin (BH4) availability, essential for dopamine synthesis and disrupt dopamine transporter function [38▪]. Rather than a general loss of pleasure, inflammation appears to specifically cause motivational anhedonia. This aligns with earlier findings that MDD patients with an inflammatory biomarker profile demonstrated a better antidepressant response to agents with dopaminergic mechanisms of action compared to purely serotonergic agents [49].

Recent work shows chronic IFN-α administration significantly reduces dopamine in motivational brain regions of rhesus monkeys [50▪]. In a randomized trial on depressed patients with CRP >2 mg/l and anhedonia ($N=18$), repeated doses of levodopa (L-DOPA), a dopamine precursor, produced clinically meaningful improvements in motivation (>10% vs. placebo) [51▪].

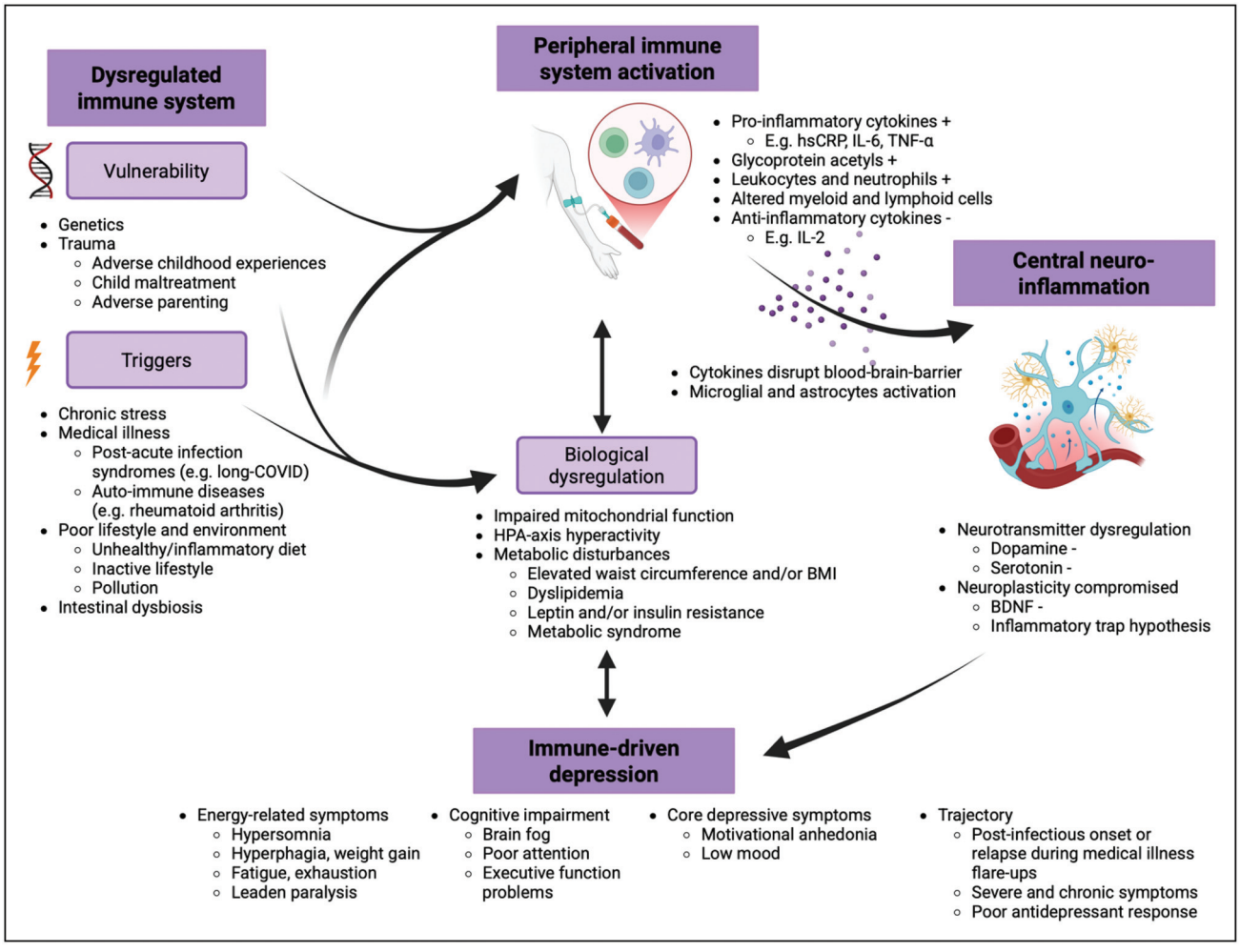

FIGURE 1. Overview of the mechanism behind immune-driven depressive symptoms, showing how vulnerabilities and triggers lead to peripheral immune activation, biological dysregulation, central neuroinflammation and ultimately depressive symptoms.

Similarly, Treadway *et al.* administered a single dose of the TNF antagonist infliximab (5 mg/kg) to depressed patients ($N=42$) with high inflammation (CRP $>$ 3 mg/l), which improved the willingness to exert effort to receive rewards, associated with activity changes in reward-related brain regions [52▪▪]. Finally, a large multicenter study ($N=108$ young adults with recent-onset depression or psychosis) identified a transdiagnostic anhedonic subgroup characterized by higher inflammatory markers and altered resting state connectivity [53▪].

Inflammation disrupts neuroplasticity

Inflammation can also impair neuroplasticity, i.e. the brain's ability to adapt and reorganize, which is crucial for recovery. Elevated pro-inflammatory cytokines have been shown to downregulate brain-derived neurotrophic factor (BDNF) and impair synaptic remodeling [54▪,55▪▪]. A conceptual framework is the *inflammatory trap* hypothesis, developed by Branchi *et al.*. This proposes that chronic inflammation locks the brain in a maladaptive, low-plasticity state that impairs response to conventional treatments, unless targeted neuroplasticity-restoring interventions are applied.

CLINICAL MANAGEMENT

Patients with an immune-driven profile show distinct treatment responses. A pooled analysis of four major clinical trials ($N=2551$) found that higher baseline CRP levels predicted smaller reductions in depressive symptoms after treatment with standard antidepressants, particularly SSRIs [16▪], replicating earlier findings of reduced responsiveness to serotonergic and noradrenergic agents in the presence of inflammation [49,56]. In contrast, dopaminergic agents such as bupropion have been linked to reductions in TNF-α and clinical improvement [57].

Interestingly, in a recent meta-analysis ($N=556$), higher levels of CRP and IL-6 were associated with better electroconvulsive therapy outcomes [58▪]. Together, these findings highlight the potential to guide the choice of antidepressants based on biomarkers, as well as the opportunity to directly target inflammation as a treatment strategy.

Lifestyle and nutritional interventions

Lifestyle interventions targeting inflammation are an attractive first-line strategy in managing immune-driven depression, as physical inactivity, poor sleep and high-sugar, high-fat Western diets contribute to the rise in inflammation-related disorders including depression [59▪]. Vreijling *et al.* compared 16 weeks of running therapy to escitalopram or sertraline in 141 patients with depression and/or anxiety. Running therapy reduced an immunometabolic depression (IMD) index (including metabolic syndrome features and inflammatory markers), while antidepressant treatment increased this index suggesting exercise can effectively target immunometabolic dysregulation [60▪]. In parallel, Yao *et al.* reviewed how exercise modulates gut microbiota composition and function, reducing systemic inflammation and improving depressive symptoms via gut-brain axis mechanisms [61▪].

The antidepressant potential of nutritional supplements targeting inflammation, such as probiotics, remain debated. For example, a recent double-blind randomized controlled trial with 75 overweight patients with depression and CRP >3 mg/l tested an 8-week adjunctive probiotic but failed to find an overall antidepressant effect [62▪]. This finding aligns with previously reported inconsistencies in the effects of probiotics on depressive symptoms and inflammation levels [63]. Omega-3 fatty acids have been more consistently linked to anti-inflammatory and antidepressant effects, although dosages, treatment durations and trial results remain variable and inconclusive [64].

Pharmacological anti-inflammatory strategies

Multiple pharmacological anti-inflammatory compounds have been investigated for the treatment of depressive disorders as summarized in Table 3.

Earlier meta-analyses have generally reported small-to-moderate antidepressant effects of these compounds, both as monotherapy and as adjunctive treatments [64]. More attention is been going to compounds with more mechanistic specificity, including dopamine-enhancing agents and low doses of IL-2, showing a shift from repurposed broader-spectrum

Table 3. Investigated pharmacological interventions targeting inflammation in depression: mechanisms, side effects and contraindications

Pharmacological intervention	Most investigated compound	Mechanism	Main side effects	Main contra-indications
NSAIDs	Celecoxib	Inhibition cyclooxygenase enzymes, reduction prostaglandin synthesis	GI discomfort, ulceration, CV risks	Peptic ulcer, cardiovascular disease, renal impairment
Antibiotics	Minocycline	Inhibition microglial activation, suppression pro-inflammatory cytokine production	Dizziness, GI discomfort, sun sensitivity	Liver dysfunction
TNF-α inhibitor	Infliximab	Blocking TNF-α (inflammatory cytokine) Inhibition of the TNF-α/TNFR1/NF-κB signaling pathway reduces microglial overactivation and neuroinflammation	Infection risk, injection-site reactions	Active infections, latent tuberculosis, demyelinating disease
IL-6 inhibitor	Tocilizumab	Blocking IL-6, modulation of downstream inflammatory pathways	Neutropenia, liver disturbances, infections	Active infections, liver disease
Low-dose IL-2	Aldesleukin	Enhance regulatory T-cell activity, restore immune homeostasis	Flu-like symptoms, autoimmunity flare-ups	Active AI disease, malignancies
GLP-1 receptor agonists	Liraglutide	Improvement metabolic dysfunction, reduction systemic inflammation	GI discomfort, pancreatitis	History of pancreatitis, medullary thyroid carcinoma

AI, auto-immune; CV, cardiovascular; GI, gastro-intestinal; IL, interleukin; MEN2, multiple endocrine neoplasia type 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF-α, tumor necrosis factor-alpha.

antiinflammatories (such as NSAIDs) toward more targeted approaches. An overview of new evidence published within the past 18 months is provided in Table 4.

However, the promising results have been tempered by RCTs that failed to demonstrate significant antidepressant effects. A common problem among past trials is the inclusion of heterogeneous populations. A promising enrichment strategy to preselect immune-driven depressed patients involves hsCRP, with several posthoc analyses showing only antidepressant efficacy in individuals with hsCRP >3 mg/l [73,74]. However, even this approach faces challenges. A recent add-on Celecoxib trial by Baune *et al.*[65▪] used a stratified design but failed to recruit sufficient patients in the high-CRP intervention arm to draw firm conclusions. Recruitment in MDD trials is already challenging, and only one third of patients present with immune-driven profiles. Adapted recruitment strategies are essential to avoid underpowered studies and to adequately test biomarker hypotheses in balanced treatment arms.

Building on these earlier efforts, several large-scale trials now apply more refined designs. For example, the INSTA-MD trial [75] uses a stratified design, comparing patients ($N=240$) with high vs. low hsCRP (≥3 or <3 mg/l) to evaluate the efficacy of add-on celecoxib and minocycline over 12 weeks. Similarly, the INSIGHT study by Khandaker *et al.* has prestratified its population based on the same CRP-cutoffs and has evaluated the IL-6 receptor inhibitor tocilizumab [76]; the trial has been completed, but results are not yet published. The inflaMED trial [77] applies an enriched design by recruiting only patients with elevated hsCRP (>1 mg/l) in combination with immuno-metabolic symptom profiles to test add-on celecoxib.

Additionally, international initiatives are aiming for a more integrative approach, recognizing that immune-driven depression probably cannot be fully captured by a single biomarker or symptom cluster. The ASPIRE study, for example, is combining clinical, biomarker, genetic, neuroimaging and transcriptomic

Table 4. Novel evidence of anti-inflammatory pharmacological interventions in major depressive disorder (2024–2025)

Trial	Compound	Duration intervention	Participants	Outcome measure	Main conclusion
Kavakbasi *et al.* 2024 [65▪] Sampson *et al.* 2025 [66▪]	Vortioxetine + celecoxib or placebo	6 weeks	119 TR MDD patients, prestratified based on hsCRP: N=80 hsCRP ≤3 mg/l *N*=39 hsCRP > 3 mg/l At 35 weeks follow-up: *N*=60 with *N*=17 hsCRP > 3 mg/l	MADRS	No significant antidepressant effect at 6 weeks, no significant effect of pretreatment CRP strata on outcome score Significant antidepressant effect at 35-week follow-up, no significant effect of pretreatment CRP strata
Nadi Sakhvidi *et al.* 2024 [67▪]	Escitalopram + celecoxib or placebo	8 weeks	60 MDD patients	HAMD-17	Significant antidepressant effect of add-on celecoxib
Esalatmanesh *et al.* 2024 [68▪]	Monotherapy celecoxib or placebo	6 weeks	50 women with postpartum depression	HAMD-17	Significant antidepressant effect of celecoxib in monotherapy
Poletti *et al.* 2024 [69▪▪]	TAU + IL-2 (aldesleukin) or placebo	5 weeks	18 MDD patients + 18 BD patients	MADRS	Significant antidepressant effect of add-on il-2
Leboyer *et al.* 2025 [70▪]	TAU + IL-2 or placebo	5 weeks	14 BD patients	MADRS	Significant antidepressant effect of add-on il-2
Eshkevari *et al.* 2024 [71]	IV ketamin + IV gluthatione or placebo	2 weeks	30 treatment resistant MDD patients	PHQ-9	No significant antidepressant effect of add-on gluthatione
Merza Mohammad *et al.* 2024 [72▪]	Citalopram + pentoxyfilline or placebo	12 weeks	100 MDD patients	HAMD-17	Significant antidepressant effect of add-on pentoxifylline

BD, bipolar disorder; CRP, C-reactive protein; HAMD-17, 17-item Hamilton Depression Rating Scale; hsCRP, High-sensitivity C-reactive protein; IL-2, interleukin-2; IV, intravenous; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; PHQ-9, 9-item Patient Health Questionnaire; TAU, treatment As usual; TR, Treatment-resistant.

trial data to develop a reproducible biological signature that can reliably identify individuals with immune-related depressive subtypes [78].

FUTURE CHALLENGES

The future of psychiatric practice lies in more precise, biologically grounded approaches, such as mechanism-based treatments for the immune-driven subgroup of patients with MDD. However, the discussed studies highlight an ongoing challenge: a lack of well designed and well powered trials with consensus on how to identify immune-driven depressions. This is a critical next step [1▪▪,3▪].

Adding to this complexity, traditional standardized outcome measures (e.g. MADRS, HAMD-17) for depression usually fail to capture the atypical symptoms linked to inflammation, such as motivational anhedonia, hypersomnia, hyperphagia or leaden paralysis. Together with the exclusion of patients with comorbid inflammatory disorders, this has led to underrepresentation or exclusion of patients who may benefit most. Potential treatment effects may not have been accurately captured either.

Miller *et al*. stress the importance of a new trial design framework in psychiatry, which includes enriching patient samples based on predictive biomarkers and using outcome assessments that align with the pathophysiological mechanisms. Integrating these strategies will be essential to advance precision psychiatry and truly realise the promise of tailored, mechanism-based treatments [1▪▪].

CONCLUSION

Evidence indicates that inflammation mechanistically contributes in about one third of depressed patients. When assessing patients, clinicians may consider pragmatic indicators such as hsCRP, comorbid metabolic or inflammatory conditions and motivational anhedonia when assessing patients, which may reflect immune-metabolic disturbances disrupting neural circuits regulating mood, energy and motivation.

Anti-inflammatory pharmacological compounds show promising antidepressant results and are leading the shift towards precision psychiatry, while lifestyle measures that reduce inflammation represent a safe and broadly applicable recommendation within standard care, even as formal guidelines for immune-based interventions are still awaited. Further progress will depend on integrating mechanistic insights, refined trial designs and inflammation-specific outcomes to move the field toward truly mechanism-based, personalized care.

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Conflicts of interest

There are no conflicts of interest.

Disclosure: The anti-inflammatory compounds discussed in this manuscript are not yet FDA-approved for the treatment of depression; their use in this context is off-label.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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Narrative review highlighting inflammation as a cross-diagnostic mechanism in psychosis, depression, and autism, identifying IL-6, T-cell regulation, immune-metabolic function, and complement as priority targets for translational research and future precision treatments.

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9. ▪ Solomon P, Budde M, Kohshour MO, *et al.* Disease severity across psychiatric disorders is linked to pro-inflammatory cytokines. Brain Behav Immun 2025; 129:359–372.

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