

Commentary

Targeting Neuroinflammation in Difficult-to-Treat Depression: From Anti-Inflammatory Agents to Multi-Target Immunopsychiatric Interventions

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Abstract

Difficult-to-treat depression (DTD) with inflammatory features (e.g., hs-CRP ≥ 3 mg/L and/or elevated IL-6) may represent a clinically and biologically distinct presentation characterized by chronicity, functional impairment, prominent cognitive-motivational symptoms, and suboptimal response to conventional treatments. Classical anti-inflammatory strategies (e.g., COX-2 inhibitors or cytokine-targeting biologics) have shown signals of efficacy in selected biomarker-enriched subgroups; however, overall evidence remains heterogeneous, with modest effect sizes and substantial limitations for real-world implementation. This Commentary advances a complementary perspective, proposing that in many patients “inflamed DTD” reflects not only increased pro-inflammatory drive but also impaired physiological resolution mechanisms across immune, autonomic, circadian, and metabolic systems. Within this “resolution failure” framework, we discuss emerging therapeutic targets and multimodal strategies and their integration into endotype-guided immunopsychiatric care. We further address limitations of the current evidence base, outline biomarker-enriched trial designs with patient-centred outcomes (functioning, quality of life, cognition), and highlight real-world barriers, including access to biomarkers, reimbursement, and equity of care. Overall, this perspective argues for moving beyond single-pathway anti-inflammatory approaches towards pragmatic, mechanistically informed interventions for inflamed DTD.



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Keywords

Difficult-to-treat depression; neuroinflammation; immunopsychiatry; melatonin; kynurenine; vagus nerve stimulation

1. Introduction: From DTD to “Inflamed DTD”

Difficult-to-treat depression (DTD) denotes patients with a chronic and recurrent course, high medical, metabolic, and psychiatric comorbidity, multiple treatment failures, and persistent functional impairment [1, 2]. In a clinically meaningful proportion of these cases, low-grade systemic inflammation can be documented, with elevations in hs-CRP, IL-6, TNF- α , IL-1 β , and other pro-inflammatory cytokines compared with both healthy controls and patients with less complex depressive episodes. In these inflammatory presentations, microglia appear chronically “primed” and biased toward a pro-inflammatory phenotype, with increased release of inflammatory mediators [3, 4]. These mediators, in turn, modulate monoaminergic and glutamatergic systems, contributing to hallmark features of inflammatory depression such as anhedonia, psychomotor slowing, and cognitive deficits. Concurrently, chronic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, with glucocorticoid resistance, and disturbances of synaptic homeostasis within fronto-striatal and limbic circuits implicated in motivation and affective regulation have been described [5]. On this basis, it is reasonable to posit an “inflamed DTD” endotype (DTD accompanied by elevated inflammatory biomarkers) as a prime candidate for targeted immunopsychiatric strategies [6, 7]. This working hypothesis underpins the present Commentary. Prior work has proposed a framework centered on identifying the “inflamed” endotype via peripheral biomarkers and reorganizing clinical pathways to enable early recognition and stratification of inflamed DTD [8]. Here, we shift the focus from “who” and “where” to “what to do,” discussing innovative therapeutic strategies that extend beyond classical anti-inflammatory agents (e.g., COX-2 inhibitors, anti-TNF, anti-IL-6 therapies) to target pro-resolving mechanisms and neuro-immune-motivational circuits. We argue that, in a subset of DTD, the core problem may not only be an excess of pro-inflammatory signaling, but also a failure of physiological resolution mechanisms involving microglia, the immune-pineal axis, the microbiota-gut-brain axis, vagal modulation, and circadian rhythms. This perspective supports exploring interventions that modulate kynurenine-glutamate circuitry, PPAR- γ signaling, melatonergic pathways, vagal circuits, and the microbiome, either as stand-alone approaches or in combination with established immunopsychiatric strategies. We hypothesize that a clinically meaningful subset of DTD is characterized by low-grade systemic inflammation and, crucially, by impaired physiological resolution mechanisms rather than pro-inflammatory drive alone. On this basis, this Commentary shifts the focus from “who to stratify” to “what to do” by outlining mechanistically informed, endotype-guided, multi-target immunopsychiatric strategies that integrate pharmacological, neuromodulatory, circadian-melatonergic, and microbiota-directed interventions, and by highlighting trial designs and implementation barriers relevant to real-world care.

2. “Inflamed DTD” as a Failure of Inflammatory Resolution

Clinically, DTD tends to cluster patients with a very long and recurrent illness course, a high lifetime burden of stressful events, frequent early-life trauma (ELT), metabolic comorbidities (obesity, metabolic syndrome, insulin resistance), and persistent disability despite multiple treatment attempts [9]. This phenotype is fairly consistently associated with chronic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis with glucocorticoid resistance, a potentially sustained elevation of hs-CRP, IL-1 β , IL-6, and TNF- α , and a “primed” microglial state, i.e., a phenotype that is more readily reactivated by subsequent challenges. A central feature of this framework is the transition of microglia from a ramified surveillance state to an amoeboid effector state, accompanied by increased release of IL-1 β , IL-6, and TNF- α and activation of pro-inflammatory transcription factors such as NF- κ B and AP-1 [10, 11]. This configuration may sustain a self-amplifying inflammatory cascade that perturbs synaptic homeostasis within fronto-striatal and limbic circuits involved in motivation, reward processing, and affective regulation. Collectively, these data suggest that, in “inflamed DTD”, the problem is not only an excess of pro-inflammatory signaling but, critically, a reduced efficiency of physiological resolution systems, including:

- Immuno-pineal and extra-pineal melatonin synthesis in immune and glial cells, supporting pro-resolving signaling [10-12].
- Microbiota-derived SCFAs, particularly butyrate, with immunometabolic and epigenetic effects relevant to resolution [13, 14].
- The vagal cholinergic anti-inflammatory reflex, linking autonomic tone, inflammation, and symptom domains [15, 16].
- Circadian organization of melatonin and cortisol rhythms and sleep-wake integrity, which influence immune regulation and recovery processes [14].

This conceptual framework lends itself to operationalization into a workflow to guide the identification and management of inflamed difficult-to-treat depression (Box 1).

Box 1 Proposed pragmatic workflow for inflamed DTD (stepwise).

1. Step 1 — Identify DTD using a multidimensional, longitudinal framework (symptoms, recurrence/chronicity, functioning, treatment history, comorbidities).
2. Step 2 — Screen inflammation with hs-CRP (and IL-6 where available); document key confounders (BMI/obesity, smoking, medications, acute infection).
3. Step 3 — Endotype refinement (as feasible): immunometabolic profile (metabolic syndrome/insulin resistance), circadian/sleep phenotype, autonomic/vagal indices (e.g., HRV), and gut-related signals (permeability/LPS proxies; SCFA/butyrate-related measures).
4. Step 4 — Match multi-target interventions and plan combinations based on the dominant mechanism (melatonergic/circadian support; taVNS; microbiota-directed strategies; immunometabolic modulation; selected anti-cytokine approaches in highly inflamed cases).
5. Step 5 — Outcomes beyond symptom scores: functioning/disability, quality of life, and cognition; use validated tools and repeated measures to track target engagement and real-world benefit.

3. Beyond Classical Anti-Inflammatory Agents: Emerging Targets for “Inflamed DTD”

This section provides a narrative overview of emerging strategies, emphasizing biological rationale, signals of efficacy, methodological limitations, and safety considerations. For transparency and synthesis purposes, key studies already cited in this manuscript are summarized in Table S1 (Supplementary Materials), including study design, biomarker enrichment, and level of evidence.

3.1 Kynurenine-Pathway Modulation and Glutamatergic Interventions

During inflammatory states, activation of indoleamine-2,3-dioxygenase (IDO1) and tryptophan-2,3-dioxygenase (TDO) diverts tryptophan away from serotonin synthesis toward kynurenine metabolites [17]. This can increase quinolinic acid (an NMDA agonist) and reduce kynurenic acid (a functional antagonist), providing a mechanistic bridge between peripheral inflammation and central glutamatergic dysregulation [18], evidence, and limitations. Preclinical studies indicate that pharmacological inhibition of IDO can attenuate inflammation-related depressive-like behavior and normalize kynurenine-tryptophan indices. However, dedicated biomarker-enriched psychiatric trials of IDO/TDO inhibitors are currently lacking. Ketamine/esketamine offers rapid glutamatergic modulation and may indirectly reduce inflammatory signaling, yet evidence specific to inflamed DTD remains limited, and trial heterogeneity is substantial [19], safety/feasibility. Ketamine/esketamine requires structured monitoring (e.g., for transient dissociation, blood pressure increases, misuse potential). For emerging IDO/TDO modulators, psychiatric safety and long-term tolerability remain open questions in this indication.

3.2 Immunometabolic Interventions and PPAR- γ Agonism

PPAR- γ agonists (e.g., pioglitazone) exert immunometabolic effects, improving insulin sensitivity and modulating low-grade inflammation. Meta-analytic evidence suggests that adjunctive pioglitazone can reduce depressive symptoms in some populations, with signals that may be stronger in immunometabolic phenotypes; however, findings are heterogeneous and often limited by small sample sizes, short duration, and weak biological stratification [20]. Evidence and limitations. Many trials do not require inflammatory biomarker elevation for inclusion, do not implement serial inflammatory measurements, and may conflate “metabolic-driven” inflammation with depression-linked inflammation. Recent data suggest hs-CRP may not track depression severity in drug-naïve obese patients with metabolic syndrome, reinforcing the need for careful phenotyping and confounder modeling [21]. Safety/feasibility. Class-related risks include weight gain, fluid retention/edema (with caution in heart failure), and fracture risk; these considerations argue for endotype-guided selection and combination approaches rather than broad, non-stratified use [22].

3.3 Melatonin and Circadian Regulation of Inflammation

Beyond its classically recognized role in sleep regulation, melatonin contributes to the modulation of inflammation through the so-called immuno-pineal axis. During an inflammatory response, pineal melatonin synthesis is transiently suppressed, while extra-pineal melatonin production increases in immune cells (e.g., macrophages) and other compartments, where it acts as a pro-resolving molecule, exerting antioxidant effects and modulating pro-inflammatory

pathways, including NF- κ B signaling [10-12]. In “inflamed DTD”, sleep disturbances, alterations in melatonin/cortisol rhythms, and chronic inflammatory burden may impair the efficiency of this axis, thereby contributing to a “block” in inflammatory resolution. This framework opens the rationale for:

- prolonged-release melatonin as an add-on treatment in DTD with insomnia and an inflammatory profile;
- melatonergic agonists (e.g., agomelatine).

Clinical evidence specifically addressing inflamed DTD remains limited; however, the convergence of data linking melatonin, inflammation, and synaptic plasticity positions this axis among the most plausible targets for future biomarker-enriched clinical trials [14].

3.4 Transcutaneous Auricular Vagus Nerve Stimulation and the Cholinergic Anti-Inflammatory Reflex

Transcutaneous auricular vagus nerve stimulation (taVNS) modulates the cholinergic anti-inflammatory reflex. Activation of efferent vagal pathways induces acetylcholine release, which, upon binding to $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChR) on macrophages, attenuates NF- κ B activation and reduces the production of pro-inflammatory cytokines, including TNF- α and IL-6. This mechanistic framework supports the potential role of taVNS as a suitable intervention in DTD characterized by reduced vagal tone, sleep disturbances, and low-grade inflammation [16]. Available studies suggest that taVNS exerts moderate antidepressant effects with a highly favorable safety profile; several reports also describe reductions in hs-CRP levels and improvements in heart rate variability (HRV), the latter serving as an indirect marker of enhanced vagal tone. In “inflamed DTD”, taVNS may be conceptualized as an intervention aimed at modulating inflammatory resolution, particularly when integrated into combined treatment protocols including antidepressants, melatonin or melatonergic agonists, and potentially future microbiota-targeted interventions along the gut-vagus-brain axis [16, 23].

3.5 Microbiota-Targeted Interventions (Psychobiotics, FMT)

In patients with major depressive disorder (MDD), a substantial body of evidence documents gut dysbiosis, reduced production of SCFAs, particularly butyrate, and increased intestinal permeability, with potential translocation of lipopolysaccharide (LPS) and other DAMPs/PAMPs into the systemic circulation [13]. Emerging clinical studies indicate that certain multistrain probiotics (psychobiotics), when used as add-on treatments, can reduce depressive symptom severity compared with placebo and modulate inflammatory markers. In parallel, faecal microbiota transplantation (FMT) has shown promising signals in small samples; however, it remains an experimental procedure associated with non-negligible risks, including infectious transmission and unpredictable adverse reactions. Within the framework of “inflamed DTD”, microbiota-targeted interventions may be conceptualized as long-term modulators of systemic inflammatory tone and antidepressant responsiveness, particularly when combined with an anti-inflammatory diet and structured physical activity [13, 14]. At present, FMT should remain restricted to rigorously regulated research settings.

3.6 Rational Combinations and Integrated Treatment Packages

Given the multi-system nature of impaired resolution (immune, metabolic, autonomic, circadian, gut-related), a single agent is unlikely to yield durable benefits in the most complex DTD presentations. A pragmatic direction is the development of integrated packages, such as:

- Targeted immunomodulation (e.g., anti-TNF/anti-IL-6 in highly inflamed subsets) combined with rapid glutamatergic interventions (ketamine/esketamine) to support synaptic plasticity restoration.
- Immunometabolic strategies (PPAR- γ agonism) integrated with Mediterranean-style diet, structured exercise, and selected psychobiotics in immunometabolic endotypes.
- taVNS combined with melatonergic/circadian stabilization and trauma-focused psychotherapy in stress/ELT-associated profiles characterized by insomnia and low vagal tone.

Evidence remains limited, and these combinations are largely hypothesis-driven at present; systematic testing in phase II biomarker-enriched proof-of-concept designs (including adaptive or factorial approaches) is therefore a research priority. These mechanistic nodes, candidate biomarkers, and corresponding multi-target interventions discussed above are summarized in Table 1.

Table 1 Inflamed DTD as “failure of resolution”: mechanistic nodes, biomarkers, and multi-target interventions.

Resolution-failure node (what is “stuck”)	Readouts to consider (triage/target engagement)	Candidate interventions (examples)	Evidence type (summary)	Typical parameters (illustrative)	Key risks/limitations
Kynurenine-glutamate axis (IDO/TDO activation; ↑ quinolinic acid; glutamatergic dysregulation)	KYN/TRP ratio; (where available) QA/KA; hs-CRP, IL-6	IDO/TDO modulation (developmental); ketamine/esketamine as rapid glutamatergic modulation; rational combinations	Preclinical strong for IDO; psychiatric trials lacking; ketamine evidence established in TRD (not specific to inflamed DTD)	Ketamine/esketamine per approved protocols	IDO/TDO inhibitors: limited psychiatric RCT data; ketamine: dissociation, BP increase, misuse risk; heterogeneity of biomarker stratification
Immunometabolic dysregulation (obesity/MetS/IR sustaining low-grade inflammation)	BMI, waist, HOMA-IR/glucose; hs-CRP; lipids	PPAR-γ agonism (e.g., pioglitazone); lifestyle package (diet/exercise) as core “resolution support.”	RCTs/meta-analyses in depression show mixed-modest benefit; signal may be stronger in immunometabolic phenotypes	Pioglitazone is often given at 15-30 mg/day in depression trials	Weight gain, edema/CHF risk, fracture risk; confounding: hs-CRP may reflect MetS more than depression (interpretation issue)
Melatonergic/circadian resolution (immuno-pineal axis dysregulation; sleep-circadian disruption)	Sleep phenotype; circadian proxies; (research) nocturnal melatonin profile, CAR	Melatonin PR; agomelatine; circadian stabilization (sleep interventions)	Mechanistic literature is substantial; clinical DTD-inflamed-specific trials are limited	Melatonin PR (night); agomelatine per label	Agomelatine: LFT monitoring; evidence gap for biomarker-enriched DTD designs
Vagal anti-inflammatory reflex (blunted cholinergic anti-inflammatory signaling)	HRV (proxy); hs-CRP, IL-6; sleep indices	taVNS (adjunct; “resolution modulation”)	Early RCTs/clinical studies suggest a moderate antidepressant signal; some biomarker/HRV	Often 20-25 Hz, ~20-30 min/session, daily or ≥3-5×/week for several weeks (protocols heterogeneous)	Protocol heterogeneity; need sham-controlled biomarker-enriched trials; generally good tolerability

effects reported					
Gut-immune-brain interface (dysbiosis; ↓ SCFA/butyrate; ↑ permeability/LPS)	Diet; GI symptoms; (research) SCFA/butyrate readouts; permeability/LPS proxies; hs-CRP	Psychobiotics (multi-strain probiotics); prebiotic/dietary interventions; FMT (research only)	Probiotics: mixed RCT signals; FMT: preliminary/small samples, experimental	Typically 4-12 weeks in probiotic trials; FMT per research protocols	Product heterogeneity (strains/doses); modest effects; FMT: infection transmission/unknown long-term effects → restrict to regulated trials
High-inflammatory cytokine drive (subset with marked peripheral inflammation)	hs-CRP; IL-6; TNF-α; clinical “inflamed” phenotype	Classical anti-inflammatories (e.g., COX-2 inhibitors); biologics (anti-TNF/anti-IL-6) in selected cases; combination packages	Signals most consistent in inflammation-enriched subgroups; overall modest; feasibility limits	Drug-specific	Safety/cost; infection risk (biologics); trial heterogeneity; access/reimbursement constraints
Synergistic multi-target packages (multi-system resolution failure)	Multi-domain: biomarkers + functioning/QoL/cognition	Examples: biologic + ketamine; PPAR-γ + lifestyle + psychobiotics; taVNS + melatonergic + trauma-focused psychotherapy	Conceptual/mechanistic rationale strong; systematic testing limited	Protocol-dependent	Need factorial/SMART or adaptive biomarker-enriched designs; implementation and equity barriers.

Note on outcomes: trials should systematically include functioning/disability, quality of life, and cognition (e.g., SDS for disability; THINC-it for cognition; QoL instruments such as EQ-5D/SF-36 where appropriate), alongside symptom severity, and should model confounders (BMI/MetS, smoking, medications, acute inflammation).

4. Implications for Biomarker-Enriched Trial Design: Dosing, Endpoints, and Target Engagement

For PPAR- γ agonists (pioglitazone), depression trials have generally employed doses of 15-30 mg/day, typically administered once daily, over 6-12 weeks [24]. Their use requires careful safety assessment, as treatment is associated with fluid retention/edema and weight gain, warranting particular caution (or avoidance) in individuals with heart failure and in patients at increased risk of fractures. For transcutaneous auricular vagus nerve stimulation (taVNS), clinical protocols are heterogeneous but commonly use stimulation frequencies in the 20-25 Hz range, with sessions lasting approximately 20-30 minutes, delivered daily or several times per week, over treatment periods typically lasting several weeks [25]. For psychobiotics (“psychoactive” probiotics), trials predominantly use multi-strain formulations for periods often ranging from 4 to 12 weeks, with good tolerability; however, the evidence base is limited by substantial heterogeneity and insufficient standardization regarding strains, dosing, duration, and biological outcomes. In future studies of “inflamed DTD”, beyond traditional depressive symptom outcomes, it is methodologically appropriate to systematically include quality of life (e.g., EQ-5D, SF-36/SF-12), functioning/disability (e.g., the Sheehan Disability Scale), and measures of cognition and motivation (e.g., THINC-it and targeted assessments of anhedonia/effort) [26]. In biomarker-enriched designs, serial assessments should include, at a minimum, hs-CRP/IL-6 and metabolic indices and, when relevant to the mechanistic hypothesis, microbiota/SCFA-related parameters and circadian markers (e.g., dim-light melatonin onset, cortisol awakening response) to link clinical endpoints to modulation of “resolution” pathways.

5. Implementation Barriers, Reimbursement, and Equity

Extended inflammatory panels (cytokines; kynurenine indices), SCFA and microbiome measures, and circadian profiling remain restricted mainly to specialist or research settings. High-cost interventions (biologics; ketamine/esketamine; combined multi-modal protocols) pose sustainability and reimbursement challenges for public health systems, while formal training in immunopsychiatry is not yet widespread.

To promote equitable translation, a tiered approach may be helpful:

- A basic level feasible in community mental health services: hs-CRP ($\pm$ IL-6, TNF- α , IL-1 β), clinical motivational/cognitive phenotype, immunometabolic assessment, and lower-cost adjuncts (psychotherapy, lifestyle interventions, selected psychobiotics, taVNS where available).
- An advanced level in tertiary/university centers: biomarker-enriched trials of novel IDO/TDO agents, next-generation PPAR ligands, combinations with ketamine and/or biologics, and detailed target-engagement measures (SCFAs, circadian markers, HRV, and where available neuroinflammation imaging).

Equity should be treated as a design constraint: endotype-based care pathways must remain accessible beyond high-resource centers to avoid widening outcome disparities.

6. Future Directions

Future research should broaden the biological sampling frame beyond single inflammatory markers and include systemic and circadian processes that plausibly sustain resolution failure in “inflamed DTD”. From a trial-design perspective, future trials should move beyond single-marker

enrichment strategies and adopt composite, mechanistically informed stratification schemes that capture both inflammatory burden and resolution capacity. Priorities include gut microbiome composition and function (including butyrate-related readouts), indices of gut permeability and endotoxin translocation, and circadian profiling of melatonin and cortisol dynamics. Mechanistically, vagal anti-inflammatory pathways may depend on the capacity to upregulate local melatonin production in peripheral tissues, while pro-resolving transitions at the CNS-immune interface may involve melatonergic regulation of transcriptional programs and microglial phenotype switching [10-16]. Finally, obesity and metabolic syndrome should be explicitly modeled as confounders or effect modifiers when interpreting hs-CRP and designing enrichment strategies [21], as inflamed DTD may represent a privileged clinical testbed in which to study the interaction between inflammatory drive and resolution failure, with implications extending beyond depression to other chronic inflammatory and neuropsychiatric conditions.

7. Conclusions

Inflamed DTD represents an even higher-burden clinical subgroup, in which low-grade inflammation, immunometabolic vulnerability, motivational dysfunction, and cumulative stress/early-life trauma intersect with years of illness course and medical-psychiatric comorbidity. In this context, merely “adding an anti-inflammatory” is at risk of being conceptually and clinically insufficient. The available evidence is heterogeneous and does not unequivocally support the notion that the therapeutic goal should invariably be limited to suppressing inflammation. In a subset of studies, the persistence of the “inflamed” phenotype is interpreted primarily as a manifestation of impaired physiological resolution mechanisms, involving integrated circuits such as the tryptophan-kynurenine pathway, the immune-pineal/melatonergic axis, the microbiota-gut-brain axis, and the cholinergic modulation characteristic of vagal anti-inflammatory pathways.

A coherent research agenda should therefore develop trials enriched for biomarkers of both inflammation and resolution (e.g., SCFAs, melatonin-related measures, HRV), systematically test emerging therapeutic targets (IDO/TDO modulation, PPAR- γ signaling, melatonergic agents, taVNS, psychobiotics, and rational combinations involving ketamine and biologics), adopt patient-centered endpoints (functioning, quality of life, cognition), and address logistical, economic, and equity barriers to implementation from the outset. Rather than merely switching off inflammation, the future of immunopsychiatry in DTD lies in restoring the biological programs that actively terminate it, through endotype-guided, multi-target strategies that translate mechanistic insights into meaningful clinical benefit.

Author Contributions

Walter Paganin conceptualized the framework, conducted the literature review, and drafted the manuscript. He critically revised the manuscript for important intellectual content and approved the final version, assuming responsibility for all aspects of the work.

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Competing Interests

The author declares no conflict of interest related to this work.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Key studies already cited in this manuscript, including study design characteristics, biomarker enrichment, and level of evidence (LOE).

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