Inflammatory Biomarkers and Treatment-Resistant Depression: A Targeted Review of Recent Clinical Evidence

Enque Endeshaw, MD [1]; Ishani Mehta, MD [2]; Amun Mustafa, MBBS [3]; Ashwin Mathai, MD [1]

[1] - Saint Elizabeths Hospital - Department of Behavioral Health, Washington, DC, USA
[2] - Maharaja Agrasen Medical College, Agroha
[3] - Fatima Memorial Hospital - College of Medicine and Dentistry, Lahore, Pakistan.

Background

- TRD affects up to 1/3 of MDD patients.
- Evidence supports the role of chronic low-grade inflammation in antidepressant non-response
- Peripheral biomarkers may guide precision psychiatry strategies.

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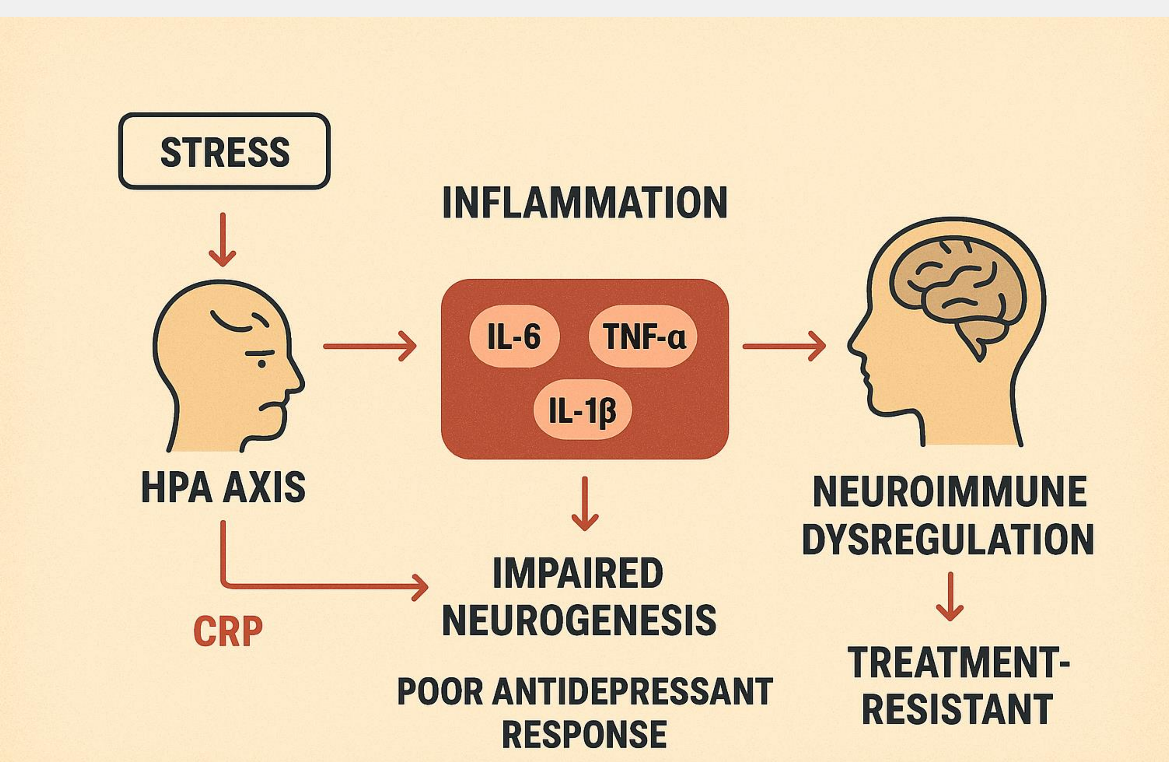


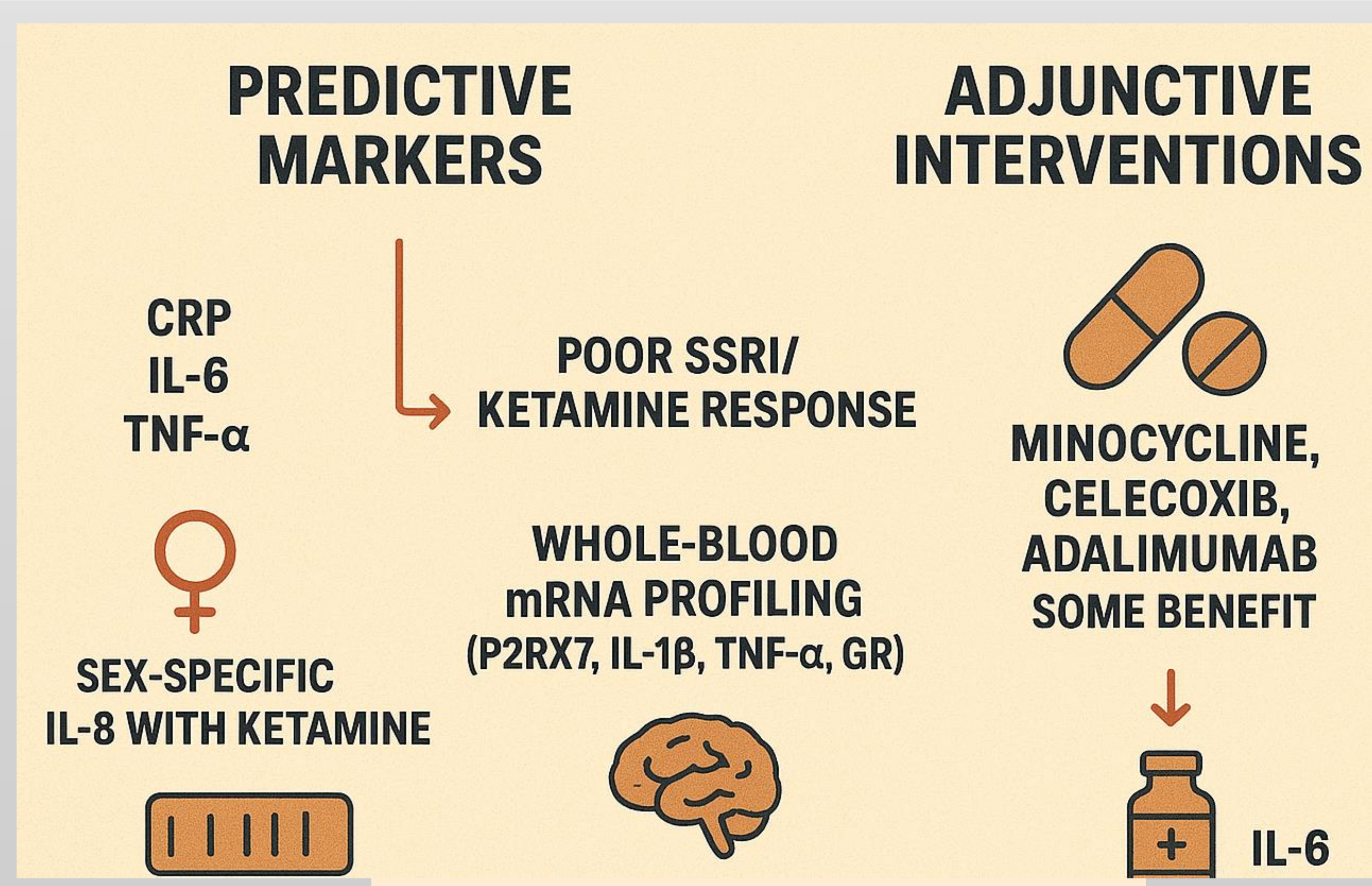
Methods

- Targeted narrative review (PubMed, Google Scholar, 2020–2025).
- 16 clinical studies: RCTs, observational, and meta-analyses.
- Inclusion criteria were limited to human studies examining the relationship between peripheral biomarkers (e.g., CRP, cytokines, BDNF), treatment response, and inflammation-targeted interventions in TRD.

Results

Inflammatory Biomarkers and Antidepressant Response Patterns in MDD

Biomarker	Associated Inflammation Type	Implication for Antidepressant Response	Potential Adjunctive Treatment
CRP (>3 mg/L)	Systemic low-grade inflammation	Poor response to SSRIs/SNRIs	Dopaminergic agents (e.g., bupropion), anti-inflammatory strategies - Adalimumab
IL-6	Pro-inflammatory cytokine	Linked to chronic stress-related depression	IL-6 inhibitors, omega-3s
TNF-α	Acute-phase cytokine	Associated with treatment non-response	TNF-α blockers (Adalimumab), lifestyle intervention
IFN-γ	Immune activation marker	May correlate with melancholic features	Limited evidence – under investigation
IL-1β	Neuroinflammatory cytokine	May impair neurogenesis and affect mood	Exercise, NSAIDs (selective use)



Kyn/tryptophan may predict ketamine response

❖ Predictive Markers
- ↑ CRP, IL-6, TNF-α → poorer SSRI/ketamine response.
- IL-8: sex-specific; ↑ after ketamine = improved response in females, worse in males.
- Whole-blood mRNA profiling (P2RX7, IL-1β, TNF-α, GR) > conventional serum cytokines.
- EEG vigilance predicts ketamine response.
- Kynurenine/tryptophan ratio → predicts ECT antianhedonic outcomes.
- Higher baseline BDNF may predict ECT response in TRD

❖ Adjunctive Interventions
- Minocycline, celecoxib, adalimumab → potential benefit in subsets.
- Metyrapone: may worsen depression, ↑ IL-6 (HPA axis activation).
- Stratification by inflammatory status → improved adjunctive response.

Conclusion

- Inflammatory biomarkers may help predict TRD risk and inform adjunctive therapies.
- Novel approaches (mRNA expression, kynurenine pathway, EEG) may enhance stratification.
- However, studies so far show inconsistent results either due to smaller sample sizes or study design limitations.
- Next step: Large, standardized trials needed for biomarker-guided care.