

## Monoclonal Antibodies and the Rise of Precision Immunopsychiatry

The emergence of monoclonal antibodies (mAbs) in psychiatry signals a paradigm shift toward precision psychiatry an approach that targets specific biological mechanisms underlying mental illness, particularly neuroinflammation and protein aggregation, rather than relying solely on modulation of neurotransmitter systems. Long established in oncology and autoimmune medicine, mAbs are now transitioning from experimental constructs to clinically relevant interventions across psychiatric and neuropsychiatric disorders <sup>1,2</sup>.

This evolving field often termed immunopsychiatry challenges the traditional "one-size-fits-all" model of psychopharmacology. By selectively targeting cytokines, immune pathways, and pathological proteins, mAbs offer a mechanistically grounded strategy for patients who do not respond to conventional antidepressants or antipsychotics. This shift reflects a broader reconceptualization of mental disorders as, in part, disorders of systemic and central immune dysregulation. Nowhere is this more evident than in Treatment-Resistant Depression (TRD). Accumulating evidence indicates that approximately 30% of patients with major depressive disorder exhibit elevated inflammatory markers, including C-Reactive Protein (CRP). In this subgroup, depression appears to be driven at least in part by low-grade systemic inflammation that influences central nervous system function. Monoclonal antibodies provide a targeted means of modulating this immune component <sup>1</sup>.

Clinical investigations have focused on cytokine inhibition as a therapeutic strategy. Tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitors such as Infliximab have demonstrated antidepressant effects in patients with elevated baseline inflammation, though not in unselected populations. Similarly, interleukin-targeting agents including Sirukumab and Ixekizumab are under active investigation. These findings underscore a critical principle: the efficacy of mAbs in psychiatry is contingent upon biomarker stratification. Patients with CRP levels exceeding approximately 3–5 mg/L appear most likely to benefit, reinforcing the necessity of personalized treatment algorithms <sup>1</sup>.

A parallel shift is underway in schizophrenia research, where low-grade inflammation is increasingly implicated in the pathophysiology of psychosis. Emerging models highlight the roles of microglial activation and B-cell-mediated immune processes. In this context, the interleukin-1 $\beta$  inhibitor Canakinumab has shown promise. A recent randomized controlled trial reported reductions in both inflammatory markers and psychotic symptom severity among biomarker-selected patients, supporting the feasibility of immune-targeted interventions in psychotic disorders <sup>2-5</sup>.

The most advanced clinical applications of mAbs lie at the intersection of psychiatry and neurology, particularly in Alzheimer's Disease (AD). Agents such as Lecanemab and Donanemab exemplify a disease-modifying approach by facilitating the clearance of amyloid- $\beta$  plaques. These therapies are now established for early-stage disease, with evidence suggesting that initiation during prodromal phases may substantially enhance efficacy. However, their use is accompanied by notable risks, including Amyloid-Related Imaging Abnormalities (ARIA), necessitating careful patient selection and monitoring <sup>6,7</sup>.

Taken together, these developments mark the transition of monoclonal antibodies from theoretical promise to clinical reality in psychiatry. The central challenge ahead lies not only in refining these therapies but in integrating biomarker-driven stratification into routine psychiatric care. Precision immunopsychiatry offers a compelling framework but its success will depend on rigorous clinical validation, equitable access, and the continued convergence of neuroscience and immunology.

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### References

1. Abbasian F, Bagheri S, Moradi K, Keykhaei M, Etemadi A, Shalbafan M, et al. Evidence for Anti-inflammatory Effects of Adalimumab in Treatment of Patients with Major Depressive Disorder: A Pilot, Randomized, Controlled Trial. *Clin Neuropharmacol* 2022;45(5):128-134.
2. Motamed M, Karimi H, Sanjari Moghaddam H, Taherzadeh Boroujeni S, Sanatian Z, Hasanzadeh A, et al. Risperidone combination therapy with adalimumab for treatment of chronic schizophrenia: a randomized, double-blind, placebo-controlled clinical trial. *Int Clin Psychopharmacol* 2022;37(3):92-101.
3. Abbasi SH, Behpournia H, Ghoreishi A, Salehi B, Raznahan M, Rezazadeh SA, et al. The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res* 2010;116(2-3):101-6.

4. Akhondzadeh S, Milajerdi MR, Amini H, Tehrani-Doost M. Allopurinol as an adjunct to lithium and haloperidol for treatment of patients with acute mania: a double-blind, randomized, placebo-controlled trial. *Bipolar Disord* 2006;8(5 Pt 1):485-9.
5. Ghaleiha A, Ghyasvand M, Mohammadi MR, Farokhnia M, Yadegari N, Tabrizi M, et al. Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial. *J Psychopharmacol* 2014;28(7):677-85.
6. Jafari P, Ghanizadeh A, Akhondzadeh S, Mohammadi MR. Health-related quality of life of Iranian children with attention deficit/hyperactivity disorder. *Qual Life Res* 2011;(1):31-6.
7. Kouti L, Noroozian M, Akhondzadeh S, Abdollahi M, Javadi MR, Faramarzi MA, et al. Nitric oxide and peroxynitrite serum levels in Parkinson's disease: correlation of oxidative stress and the severity of the disease. *Eur Rev Med Pharmacol Sci* 2013; 17(7):964-70.