

VALPROATE IS ASSOCIATED WITH LOWER INFLAMMATORY BURDEN IN EUTHYMIC BIPOLAR DISORDER: EVIDENCE FROM NOVEL COMPOSITE INFLAMMATORY INDICES

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BACKGROUND AND AIM: Systemic inflammation is increasingly recognized as a core component of the pathophysiology and neuroprogression of bipolar disorder (BD). Novel composite hematologic indices, including the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV), offer accessible measures of the inflammatory burden. However, the effects of mood stabilizers on these parameters remain unclear. This study aimed to examine the association between lithium and/or valproate (VPA) treatment and systemic inflammatory burden in euthymic patients with BD.

METHODS: (Ethics Committee Approval must be obtained and the number should be specified). A total of 520 euthymic patients with DSM-5–diagnosed BD were included and classified into four groups: no lithium/VPA, VPA, lithium, and lithium+VPA. Sociodemographic and clinical variables, complete blood count parameters, and derived inflammatory indices (SII, SIRI, and PIV) were compared. This study was approved by the Ethics Committee of Necmettin Erbakan University (IRB: 2025/5925).

RESULTS: The groups were largely comparable in terms of sociodemographic features. The lithium+VPA group exhibited a more severe illness course, including longer disorder duration and higher episode and hospitalization counts (all $p \leq .001$). The VPA group demonstrated significantly lower neutrophil counts and reduced SII, SIRI, and PIV values than the lithium and no lithium/VPA groups (all $p < .001$). In the regression analysis, VPA use independently predicted lower SII levels ($\beta = -0.168$, $p = .021$), whereas lithium use showed no significant association ($p = .481$). Inflammatory indices were not correlated with illness duration, number of episodes, or hospitalization history.

CONCLUSIONS: Valproate treatment was associated with a reduced systemic inflammatory burden in euthymic BD, independent of clinical severity. In contrast, lithium was not associated with lower inflammatory indices. These findings suggest that VPA may exert an anti-inflammatory effect beyond mood stabilization, highlighting the relevance of immuno-inflammatory mechanisms in treatment selection and the long-term course of BD.

Keywords: Systemic inflammation, bipolar disorder, valproate