

## Folinic Acid Supplementation in Autism Spectrum Disorder: Mitigating Safety Concerns Amid Rising Off-Label Use

Dua Fatima Sherwani<sup>1</sup>, Syeda Abeeha Hasan<sup>1</sup>, Dua Ul Khair<sup>1</sup>, Aisha Hanif<sup>1</sup>

Jinnah Sindh Medical University, Karachi, Pakistan

Folinic acid (leucovorin) is emerging as a potential adjunct in autism spectrum disorder (ASD), driven by growing clinical evidence. A recent pediatric randomized trial by Panda et al, 2024<sup>1</sup> demonstrated modest subgroup-specific improvements; however, replication remains scarce, and broader applicability uncertain. Given the heterogeneity of ASD, biomarker-based precision and medically supervised caution are crucial.

The pivotal RCT by Frye<sup>2</sup> reported an improved verbal communication in children receiving folinic acid, particularly those positive for FR $\alpha$  autoantibodies, which is a subset of ASD cases. These autoantibodies block folate transport across the blood-brain barrier, subsequently leading to cerebral folate deficiency. Folinic acid can bypass this blocked pathway; nevertheless, we cannot yet recommend it for routine clinical use, given the need for larger-scale multisite studies with varying demographics.

Prior to widespread use and clinical adoption, several safety and clinical considerations must be addressed. First, folinic acid may reduce serum levels and efficacy of anticonvulsants (antiepileptic drugs (AEDs), typically phenytoin and phenobarbital) by increasing their hepatic metabolism and clearance, raising the risk of breakthrough seizures. Since many individuals with ASD experience seizures concurrently, the administration of folinic acid should be accompanied by ongoing therapeutic medication monitoring to ensure stable serum levels of AEDs. Second, high doses of folinic acid, particularly with prolonged use, may mask vitamin B12 deficiency. It does correct anemia, though the neurological deterioration progresses.<sup>3</sup> Proactive assessments of vitamin B12 concentrations are essential in such cases. Lastly, although polymorphisms in the *MTHFR* gene have gained public interest as a potential risk predictor for autism,<sup>4</sup> professional consensus guidelines do not support using *MTHFR* testing to guide therapy decisions, including folinic acid therapy.<sup>5</sup>

Accordingly, folinic acid use should align with a precision-medicine framework to benefit patients with positive biomarkers (FR $\alpha$  autoantibodies or metabolic/folate imbalance), although universal accessibility to these approaches remains variable, with FR $\alpha$  autoantibody testing largely limited to specialized centers. A sound registry or clinical audit that tracks patients' therapy, medications, and outcomes, along with pharmacist-clinician collaboration, protects patients and strengthens the evidence base.

Overall, even though folinic acid shows early promise in biologically defined ASD subgroups, widespread use remains premature and risks outpacing available evidence. Particular caution is warranted when supplementation is initiated without biomarker-based selection, in children receiving anti-epileptic medications, or in the absence of baseline vitamin B12 assessment. Clinician-supervised,

**Corresponding author:**

Dua Fatima Sherwani

**E-mail:**

duasherwani.05@gmail.com

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biomarker-guided, and carefully monitored implementation is essential to safely translate early promise into responsible and meaningful clinical practice.

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