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ACMT Position Statement: Use of Leucovorin for Autism Spectrum Disorder

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The position of the American College of Medical Toxicology (ACMT) is as follows:

The U.S. Food and Drug Administration (FDA) bypassed its typical rigorous evidentiary standard for approval of leucovorin for treatment of a rare, specific form of cerebral folate deficiency (CFD) that has significant overlap with autism spectrum disorder (ASD), a much more common diagnosis. FDA typically requires clinical trials for approval, but in this case the approval for the new indication was based on case reports and a mechanistic rationale. We are concerned that off-label use of this drug for ASD will increase health care costs and impact leucovorin availability for its established role in cancer treatment, methotrexate toxicity, and certain vitamin deficiencies. Patients and families affected by ASD have already been the target of pseudoscientific treatment and information. In some cases, these therapies have been harmful. ACMT supports use of leucovorin for ASD only in the context of clinical research until more supporting data becomes available. Robust FDA process for labeling changes should not be bypassed.

Background

ASD is a pervasive neurodevelopmental disorder characterized by developmental delay, deficits in social communication, motor disturbances and repetitive behaviors affecting about 3% of US children [1,2]. The etiology of ASD is poorly understood, but has been linked to a variety of environmental, perinatal, and genetic factors [1]. Despite claims associating ASD with vaccines and maternal use of acetaminophen during pregnancy, a causal link has not been established [1,3]. Treatment options are largely supportive and include developmental, social, educational, and behavioral interventions. While medications can be used as adjunctive therapy for symptom management, none have demonstrated efficacy addressing the underlying pathophysiology of ASD [4].

Cerebral folate deficiency (CFD) is a neurologic condition where there is a relative deficiency of the essential B-vitamin folate. It has a variety of etiologies, including autoimmune and genetic forms. Symptoms of CFD have significant overlap with ASD, including severe developmental delay and motor disturbances [5]. The prevalence of CFD in individuals diagnosed with ASD is poorly described.

Leucovorin is an activated form of folate that has shown promise for the treatment of CFD [1,5,6]. Originally approved in 1983, leucovorin had been used primarily as a rescue agent to reduce the toxic effects of chemotherapeutic agents such as methotrexate and other folate antagonists [7]. Leucovorin may work in CFD by delivering activated folate to the brain, bypassing dysfunctional folate receptors. Although there are data to suggest that leucovorin treatment can be beneficial for the treatment of the genetic form of CFD [6,7], data supporting the use of leucovorin for other forms of CFD and broader ASD are limited.

FDA Approval

In March 2026, FDA approved leucovorin for FOLR1-related cerebral folate deficiency (CFD-FOLR1) [8].This approval followed a September 2025 announcement where FDA proposed a labeling expansion for leucovorin for patients with nonspecific cerebral folate deficiency [9]. Following criticism that FDA had bypassed its usual supplemental New Drug Application process and approved the drug without a clinical trial, the ultimate FDA approval was narrower than suggested by the 2025 announcement [10].

The September 2025 announcement and March 2026 approval did not follow the typical pathway of a sponsor submitting an application with new clinical trial data to support the supplemental indication. Per statute, FDA must deny new drug applications if there is a lack of “substantial evidence” of effectiveness. As of 1997, federal law requires “adequate and well-controlled investigations”, which is currently interpreted to mean at least one clinical trial (prior to 1997, two such trials were required). Instead, the agency acted on published literature, case reports, and a mechanistic rationale [10].

Regulatory Issues and Predatory Practices

Bypassing established FDA regulatory processes may lead to approval of medications for treatment of conditions where they have not met a rigorous evidentiary standard. Clinical trials, which are usually required for FDA approval, provide important information to prescribers, patients, and families regarding risks and benefits of a course of therapy.

Formal FDA approval of a new indication for previously approved drugs does not necessarily expand patient access to drugs, because prescribers can already write medications off-label. (A change in labeling may influence coverage decisions by some payers.) However, FDA approval suggests a level of scientific evidentiary support and prescribers may feel pressured to prescribe leucovorin despite limited evidence of benefit. ACMT is concerned that this may distract from proven therapies. Disappointing clinical results may diminish public confidence in the FDA, medicine, and science.

Patients with ASD and families who support them have long been the target of pseudoscientific treatment and information. Popular but potentially dangerous treatments with no proven efficacy such as chelation [11],“miracle mineral solution” [12], or hyperbaric oxygen therapy [13] have

already been accepted by desperate families and patients. Additionally, the discrepancies between the initial announcement in September 2025 and the final approval in March 2026 may have caused confusion among families and healthcare providers.

Health Care Cost and Leucovorin Shortages from Increased Prescription

Expanding use of leucovorin could be costly. The recommended dose of leucovorin for CFD is 1-2 mg/kg/d. Doses up to 50 mg/d have been used in clinical trials for treatment of ASD [14]. Based on the wholesale acquisition cost of $223.53 for a 25 count of 25 mg leucovorin tablets, this therapy would cost $17.88 per day, $6,527 per year [15].

Increased demand from treating patients with ASD could lead to drug shortages and lack of leucovorin for patients for whom the drug is proven to be life-saving. A 2026 study reported a 71% increase in leucovorin prescribing in children ages 5 to 17 since September 2025 [16]. Prescription drug shortages have impacted many medications, including antidotes in recent years [17,18]. Shortages of leucovorin can impact its availability for cancer treatment, methotrexate toxicity, and certain vitamin deficiencies. There are 7 manufacturers that make parenteral leucovorin and 5 that produce oral formulations [19]. According to drug shortage data retrieved from the University of Utah Drug Information Service there have been a total 5 leucovorin shortages since 2001 [19]. Of these, 4 involved the injectable form and 1 shortage impacted oral tablets. Two of these shortages are ongoing, with one shortage of leucovorin injectable ongoing since 2010. There has been an ongoing shortage of leucovorin tablets since June 2025.

Recommendations

The American College of Medical Toxicology supports continued research on the role of folate metabolism in ASD and development of novel treatments for that condition. ACMT also recognizes that the robust framework in place for drug approval and labeling changes should not be bypassed. ACMT, along with the American Academy of Pediatrics [20] stands firmly against the premature use of leucovorin in treatment of ASD.

Disclaimer

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While individual practitioners may differ, these are the positions of the American College of Medical Toxicology (ACMT) at the time written, after a review of the issue and pertinent literature.

No Conflicts of Interest

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