



Autism Spectrum Disorder: Leucovorin Treatment

General Information

- High-dose leucovorin may have a role in treating symptoms in a subpopulation of those with autism spectrum disorder symptoms.
- Potential benefits include improvement in measures of social withdrawal, repetitive behaviors, irritability, language/communication, and ataxia. However, conclusive evidence is lacking.
- One test that has been used to assist with which patients should receive a trial of leucovorin is the test for folate receptor autoantibodies (FRAA). A +FRAA (blocking antibodies >0.5) result may support a diagnosis of cerebral folate deficiency. However, response to leucovorin can occur in those with positive or negative tests.
- FRAA testing is not covered by insurance.
- Routine testing of FRAA is not supported by the evidence. If FRAA testing is desired after treatment with leucovorin has been initiated, leucovorin must be discontinued for 2 days prior to obtaining the blood sample for testing.
- Fratnow.com (not sure what this site provides – information for families or where to send test)

Leucovorin Treatment Trial

1. Start at 0.5 mg/kg/day divided BID
 - maximum single dose = 25mg
 - maximum daily dose = 50 mg)
2. Increase the dose by 0.5 mg/kg/day divided BID every 2 weeks until the maximum dose is reached. Increase more slowly based on tolerance or baseline behavioral symptomatology).
 - Maximum weight based daily dose = 2 mg/kg/day divided BID.
 - Maximum single dose = 25 mg
 - Maximum daily dose = 50 mg

Leucovorin Pharmacology

1. Increasing the dose beyond the maximum single and daily doses will not increase the leucovorin serum levels.
2. Common side effects include
 - Paradoxical worsening of hyperactivity, inattention, irritability, insomnia, and nausea/vomiting
 - Rash
 - Allergic reactions
3. Rarely, leucovorin may lead to seizures in patient without a history of seizures. It may increase the frequency of seizures in patients known to have seizures.
4. Leucovorin may mask hematologic manifestations of B12 deficiency, so periodically measuring B12 levels rather than following CBC should be considered.



To make a referral

Norton Children's providers: Go to Epic Ambulatory

Community providers: Scan the **QR code** or call **(833) 559-7337 (PEDS)**

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User sites: Ambulatory, Neurology, Autism

Users: General Pediatrics, Neurology

Internal and external sites

Approvals

	Person	Initials and date
Autism highest ranking physician leader	Gregory Barnes, MD	GB 4/21/26
Clinical Resource Steering Committee	Vicki Montgomery, MD	VLM 4/14/26
Marketing		

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