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Leucovorin (Folinic Acid) and Autism: Information for Families

Understanding Autism and Medical Treatments

Children, teens, and young adults with Autism Spectrum Disorder are valued members of our communities. They deserve care that supports their well-being, respects their individuality, and is based on good scientific evidence.

Autism is a complex condition that develops from a mix of genetic and environmental factors. Because every child is different, there isn't one single treatment that works for everyone. Over the years, some therapies have been tried that didn't help—or even caused harm—because they weren't well studied. That's why doctors and families now focus on evidence-based care and make decisions together with care and caution.

What Is Leucovorin?

Leucovorin (also called *folinic acid*) is a prescription form of folate (vitamin B9). Unlike regular folic acid supplements, leucovorin is already in an "active" form that the body can use right away. It is prescribed in a much higher dose than over the counter folinic acid.

Doctors already use leucovorin for certain medical reasons, such as:

- Reducing side effects from chemotherapy medications like methotrexate
- Treating certain types of anemia

Researchers have also studied leucovorin in small groups of children who have a rare condition called *cerebral folate deficiency (CFD)* or in those who have specific antibodies that may affect how folate works in the brain.

Why Do Some Families Ask About Leucovorin and Autism?

Some early, small research studies have looked at whether leucovorin might help with language and communication in certain autistic children—especially those with signs of folate problems. A few small studies found encouraging results, but the research so far is too limited to make clear recommendations for all autistic children.

At this time, the **American Academy of Pediatrics (AAP)** does **not recommend leucovorin as a routine treatment for autism**. Larger, well-designed studies are still needed to understand:

- Which children might benefit
- What the safest and most effective doses are
- How to monitor long-term safety

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What Is Cerebral Folate Deficiency (CFD)?

CFD is a rare condition where the brain doesn't get enough active folate, even though blood folate levels are normal. This typically presents in infants and young children.
Children with CFD don't just have ASD—they usually have other symptoms such as developmental delays or regression, seizures, changes in muscle tone, or an abnormal neurological examination. It can occur because of genetic changes or because the body makes certain antibodies that block folate from entering the brain.

Testing for CFD is complicated and may involve spinal fluid or genetic testing, which are not needed for most children. Routine blood tests cannot confirm CFD.

What Are Folate Receptor Autoantibodies (FRAAs)?

These are proteins made by the immune system that can block folate from reaching the brain. Some research has linked FRAAs with CFD.

However, testing for FRAAs is **not standardized or FDA-approved**, and results can vary between labs. Doctors interpret these tests cautiously, as we don't yet know how well they predict who will respond to leucovorin. This test is not available in Alberta and is not recommended at this time.

What Do Studies Show So Far?

- Some small studies (under 100 children) found possible improvements in communication or behavior for a few children with ASD who were treated with leucovorin
- Most studies have come from one research group and there are questions about study methods. We need larger, independent trials to assess the effect of leucovorin.
- There is not yet a clear or proven link between leucovorin and improvement in autism overall.
- More research is needed before leucovorin can be widely recommended or prescribed routinely.

Are There Side Effects?

Leucovorin can affect each child differently. Most children tolerate it well, but possible side effects can include irritability or restlessness (*with increased aggression in ~10% of kids*), stomach upset (such as nausea, diarrhea, or loss of appetite), or, rarely, skin reactions or allergic responses.

Because studies thus far provide short term data, we have no information on potential long term side effects.

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What We Still Don't Know

Researchers are still working to answer important questions:

- How can we best identify which children might benefit?
- Do children without CFD respond to leucovorin?
- What are the safest long-term doses?
- How should progress and side effects be monitored?

Until more is known, leucovorin is considered an experimental or "off-label" option for autism, used only in carefully selected cases with close medical monitoring.

Bottom Line

- Leucovorin is not a standard treatment for autism.
- More research is needed before it can be widely recommended.
- If used, it should be prescribed and closely monitored by a doctor.
- Evidence-based supports and therapies remain the foundation of care for autistic children.
- The AAP continues to review new research and will update its recommendations as stronger evidence becomes available.

Your child's care team at Infinity Pediatrics is here to help you make the best, evidence-based choices for their health and development.

If you have further questions, talk to your child's physician.

This information is adapted from the American Academy of Pediatrics Interim Guidance on the Use of Leucovorin in Autistic Pediatric Patients (2025).